Title: A Phase 1/2 Study of the Safety, Pharmacokinetics, and Anti-Tumor Activity of the Oral EGFR/HER2 Inhibitor TAK-788 (AP32788) in Non-Small Cell Lung Cancer

NCT Number: NCT02716116

Protocol Approve Date: 02 September 2020

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

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

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

Study Title: A Phase 1/2 Study of the Safety, Pharmacokinetics, and Anti-Tumor Activity of the Oral EGFR/HER2 Inhibitor TAK-788 (AP32788) in Non-Small Cell Lung Cancer

Protocol Number: AP32788-15-101

Study Phase: Phase 1/2

Product Name: TAK-788 (formerly AP32788)

IND Reference Number: IND 126721

EudraCT Number: 2016-001271-68

Sponsor: Millennium Pharmaceuticals, Inc. (MPI)*

40 Landsdowne Street
Cambridge, MA 02139 USA
Telephone: +1 (617) 679-7000

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

Protocol Issue Date: 02 September 2020

Amendment Number: Amendment 6

1 PROTOCOL REVISION HISTORY

<table>
<thead>
<tr>
<th>Amendment Number</th>
<th>Date</th>
<th>Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amendment 6</td>
<td>02 September 2020</td>
<td>Global</td>
</tr>
<tr>
<td>Amendment 5</td>
<td>13 August 2019</td>
<td>Global</td>
</tr>
<tr>
<td>Amendment 4</td>
<td>11 October 2018</td>
<td>Global</td>
</tr>
<tr>
<td>Amendment 3</td>
<td>03 July 2018</td>
<td>Global</td>
</tr>
<tr>
<td>Amendment 2</td>
<td>02 March 2018</td>
<td>Global</td>
</tr>
<tr>
<td>Amendment 1</td>
<td>22 March 2017</td>
<td>Global</td>
</tr>
<tr>
<td>Original Protocol</td>
<td>21 November 2015</td>
<td>Global</td>
</tr>
</tbody>
</table>
3 SIGNATURE PAGES AND PROTOCOL AMENDMENT SUMMARY OF CHANGES

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.
- 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.
Investigator Signature

I have read the protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein, including all statements regarding confidentiality. I will make a reasonable effort to complete the study within the time designated. I will provide copies of the protocol and access to all information furnished by the sponsor to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study drug and the study. I understand that the study may be terminated or enrollment suspended at any time by the sponsor, with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

I agree to conduct this study in full accordance with all applicable regulations.

________________________________________________________________________
Investigator’s Signature Date (dd-mmm-yyyy)

________________________________________________________________________
Investigator’s Name (print)
## Contact Information

| Sponsor                      | Takeda Pharmaceutical Company Limited  
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>40 Landsdowne Street</td>
</tr>
<tr>
<td></td>
<td>Cambridge, MA 02139</td>
</tr>
<tr>
<td></td>
<td>USA</td>
</tr>
<tr>
<td></td>
<td>Telephone: +1 (617) 679-7000</td>
</tr>
</tbody>
</table>

| Sponsor Medical Monitor:     | PPD                                    |
Protocol Amendment 6 Summary and Rationale:

This section describes the changes in reference to the protocol incorporating Amendment 6. The primary reasons for this amendment are to:

- Update per-protocol population definition.
- Incorporate changes due to coronavirus disease 2019 (COVID-19) public health emergency including direct-to-patient (DTP) dispensing as an alternative method of dispensing self-administered study drug, alternative methods for conducting patient visits, electronic informed consent (eConsent) language, and accommodations to allow local disease assessments.
- Revise pharmacokinetic (PK) parameters and analysis.
- Update Appendix C Drugs That Interact With the CYP3A Family of Cytochromes-P450.
- Update Appendix D Drugs With a Risk of Torsades de Pointes.

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

<table>
<thead>
<tr>
<th>Protocol Amendment 6</th>
<th>Summary of Changes Since the Last Version of the Approved Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Description</td>
</tr>
<tr>
<td>Section 4 PROTOCOL SYNOPSIS</td>
<td>Revised dose linearity to dose proportionality.</td>
</tr>
<tr>
<td>Section 16.6.1 Pharmacokinetic Analysis</td>
<td>Revised dose linearity to dose proportionality.</td>
</tr>
<tr>
<td>Section 12.1 Study Procedure Descriptions</td>
<td>Update text to include alternative methods for conducting patient visits and collecting data.</td>
</tr>
<tr>
<td>Section 14.7.2 Treatment(s) Storage, Dispensing, and Accountability</td>
<td>Update text to include direct-to-patient study drug.</td>
</tr>
<tr>
<td>Section 16.2 Analysis Populations</td>
<td>Update per-protocol population definition.</td>
</tr>
<tr>
<td>Appendix C Drugs That Interact With</td>
<td>Update Appendix C Drugs That</td>
</tr>
</tbody>
</table>
## Protocol Amendment 6

### Summary of Changes Since the Last Version of the Approved Protocol

<table>
<thead>
<tr>
<th>Location</th>
<th>Description</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>the CYP3A Family of Cytochromes P450</td>
<td>Interact With the CYP3A Family of Cytochromes-P450.</td>
<td>references.</td>
</tr>
<tr>
<td>Appendix D Drugs With a Risk of Torsades de Pointes</td>
<td>Update Appendix D Drugs With a Risk of Torsades de Pointes.</td>
<td>Update for consistency with current reference.</td>
</tr>
</tbody>
</table>
4 PROTOCOL SYNOPSIS

<table>
<thead>
<tr>
<th>Property</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Millennium Pharmaceuticals, Inc. (MPI)*</td>
</tr>
<tr>
<td></td>
<td>*Please note: Millennium Pharmaceuticals is a wholly owned subsidiary of Takeda Pharmaceutical Company Limited and thereafter, any reference to the sponsor will use Takeda’s name.</td>
</tr>
<tr>
<td>Study Treatment</td>
<td>TAK-788 (formerly AP32788)</td>
</tr>
<tr>
<td>Study Title</td>
<td>A Phase 1/2 Study of the Safety, Pharmacokinetics, and Anti-Tumor Activity of the Oral EGFR/HER2 Inhibitor TAK-788 (AP32788) in Non-Small Cell Lung Cancer</td>
</tr>
<tr>
<td>Development Phase</td>
<td>Phase 1/2</td>
</tr>
<tr>
<td>Summary and Study Rationale</td>
<td>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 (i.e., 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 (WT) 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 WT EGFR.</td>
</tr>
<tr>
<td></td>
<td>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]. Erlotinib and gefitinib (“first generation” EGFR TKIs), as well as afatinib (a “second generation” EGFR TKI), potently inhibit these mutants in vitro and induce high response rates of about 60%-70% in patients with these mutations [4]. Osimertinib has recently been approved in patients with common mutations as the first-line treatment option, following the first approval in patients with metastatic EGFR T790M mutation-positive NSCLC and who have progressed on or after EGFR TKI therapy [5,6]. Although these TKIs are approved for use in patients with these specific mutations, their clinical efficacy is ultimately limited by the development of resistance, such as by mutation of the EGFR kinase domain gatekeeper residue (T790M), which occurs in 50% of patients [7,8].</td>
</tr>
<tr>
<td></td>
<td>For erlotinib and gefitinib, high response rates have largely been restricted to patients with the most common activating mutants; however, preliminary results with afatinib suggest that relatively high response rates are also achieved in patients with a second class of activating mutants, so-called “uncommon” mutants, such as those occurring at other amino acids in exons 19 and 21 (eg, G719 and L861) [9]. Afatinib was recently approved by the Food and Drug Administration (FDA) for a broadened indication in first-line treatment of patients with metastatic NSCLC whose tumors have nonresistant EGFR mutations to include patients whose tumors harbor uncommon mutations, such as L861Q, G719X, and S768I [10].</td>
</tr>
<tr>
<td></td>
<td>The final class of EGFR activating mutations, known as exon 20 insertions, account for approximately 9% of EGFR mutant NSCLC [11]. Unlike mutations in exons 19 or 21, almost all EGFR exon 20 insertions confer in vitro and primary clinical resistance to the three approved EGFR TKIs [9,12,13]. Patients with NSCLC containing EGFR exon 20 insertions exhibit clinical characteristics similar to those carrying common EGFR mutations [14] (eg, young, nonsmoker, with adenocarcinoma subtype), consistent with potential roles as driver mutations that could confer benefit to targeted therapy. In</td>
</tr>
</tbody>
</table>
summary, while erlotinib, gefitinib, afatinib, and osimertinib are approved for use in NSCLC patients with common activating mutations in EGFR (ie, exon 19 deletions and L858R substitutions) and afatinib was recently approved by the FDA for a broadened indication that includes the uncommon EGFR mutations, such as L861Q, G719X, and S768I, no targeted therapies are approved for patients with EGFR exon 20 insertions.

Human epidermal growth factor 2 (HER2) mutations, typically consisting of in-frame insertions in exon 20, have also been identified as potential oncogenic drivers in 2%-4% of NSCLC patients. These patients exhibit clinical characteristics similar to EGFR-mutated patients [15-17]. Currently, no therapies are approved for use in NSCLC patients with HER2 activating mutations.

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

Based on the promising activity profile of TAK-788 in vitro and in vivo, as well as its toxicologic profile, a phase 1/2 clinical trial of the agent is proposed. The trial will be conducted in three parts: a dose escalation phase, followed by an expansion phase and a pivotal extension phase.

**Part 1: Dose Escalation Cohorts**

The patient population of the initial dose escalation phase of the trial will include patients with advanced NSCLC. The objectives of the dose escalation phase are to determine the safety, pharmacokinetic (PK) profile, and recommended phase 2 dose (RP2D) of orally administered TAK-788 in these patients.

**Part 2: Expansion Cohorts**

The dose and schedule for the expansion cohorts will be determined based on the RP2D and schedule determined in the dose escalation phase of the trial.

The expansion phase will include seven histologically and molecularly defined cohorts. The seven expansion cohorts will be:

1. NSCLC patients with EGFR exon 20 activating insertions, who have either not received or not shown an objective response to an EGFR TKI, and who have no active, measurable central nervous system (CNS) metastases;
2. NSCLC patients with HER2 exon 20 activating insertions or point mutations and no active, measurable CNS metastases;
3. NSCLC patients with EGFR exon 20 activating insertions or point mutations and HER2 exon 20 activating insertions or point mutations and active, measurable CNS metastases;
4. NSCLC patients with other targets against which TAK-788 is active (examples include EGFR exon 19 deletions or exon 21 substitutions [with or without T790M mutations] and other uncommon EGFR activating mutations), without active CNS metastases;
5. NSCLC patients with EGFR exon 20 activating insertions, who have previously shown an objective response to or stable disease (SD) with an...
EGFR TKI and subsequently progressed, without active CNS metastases;
6. NSCLC patients with EGFR exon 20 activating insertions, who have not received prior systemic anticancer treatment for locally advanced or metastatic disease, without active CNS metastases; and
7. Patients with solid tumors other than NSCLC with EGFR/HER2 mutations against which TAK-788 is active, without active CNS metastases.

The safety and tolerability of orally administered TAK-788 will continue to be assessed in the expansion cohorts. However, the primary objective of the expansion component of the trial is to evaluate the anti-tumor activity of TAK-788 in these patient populations. Confirmed objective response rate (ORR), as assessed by the investigator per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), will be the primary endpoint in the expansion cohorts with the exception of Expansion Cohorts 3 and 6.

**Part 3: Extension Cohort**

The extension cohort is designed to evaluate the efficacy of TAK-788 at the RP2D in patients with locally advanced or metastatic NSCLC whose tumors harbor EGFR exon 20 insertion mutations and who have been previously treated. All patients in the extension cohort 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. The confirmed ORR, as assessed by Independent Review Committee (IRC) per RECIST v1.1, will be the primary endpoint in the extension cohort.

The RP2D to be used in the extension cohort was selected as 160 mg once daily (QD) based on data collected from both Parts 1 and 2 (dose escalation and expansion phases) up to August 2018.

**Study Design**

Open-label, multi-center, dose escalation study (3+3 design initial dose escalation cohort) with expansion into seven histologically and molecularly defined cohorts after the RP2D is established and a pivotal extension cohort following establishment of early proof-of-concept in patients with NSCLC with EGFR exon 20 insertion mutations.

**Study Objectives**

**Parts 1 and 2: Dose Escalation and Expansion Cohorts**

1. To determine the safety profile of orally administered TAK-788
2. To identify the RP2D, dose-limiting toxicities (DLTs), and the maximum tolerated dose (MTD) of TAK-788
3. To determine the PK profile of TAK-788 and its active metabolites, AP32960 and AP32914
4. To evaluate the anti-tumor activity of TAK-788 in NSCLC patients with EGFR or HER2 mutations
5. To evaluate the anti-tumor activity of TAK-788 in patients with solid tumors other than NSCLC with EGFR or HER2 mutations

**Part 3: Extension Cohort**

Primary: To determine the efficacy of TAK-788, as evidenced by confirmed ORR, as assessed by the IRC, in patients with locally advanced or metastatic NSCLC harboring EGFR in-frame exon 20 insertion mutations and who have received at least 1 prior line of therapy for locally advanced or metastatic NSCLC.
Secondary:
1. To further characterize the efficacy of TAK-788 as shown by confirmed ORR, as assessed by the investigator, duration of response, progression free survival (PFS), disease control rate (DCR), time to response, and overall survival (OS)
2. To assess the safety and tolerability of TAK-788
3. To collect sparse plasma concentration-time data of TAK-788 and its active metabolites, 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 (QOL)-C30 and the EORTC lung cancer module, QLQ-LC13

Study Endpoints

<table>
<thead>
<tr>
<th>Part 1: Dose Escalation Component</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Endpoint:</td>
</tr>
<tr>
<td>• RP2D of orally administered TAK-788</td>
</tr>
<tr>
<td>Secondary Endpoints:</td>
</tr>
<tr>
<td>1. Safety profile of orally administered TAK-788</td>
</tr>
<tr>
<td>2. DLTs and MTD of orally administered TAK-788</td>
</tr>
<tr>
<td>3. 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</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Part 2: Expansion Cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Endpoint:</td>
</tr>
<tr>
<td>• Investigator-assessed confirmed ORR (using RECIST v1.1), except for Expansion Cohort 3, in which intracranial ORR (iORR) (as assessed by the IRC) will be the primary endpoint, and Expansion Cohort 6, in which confirmed ORR (as assessed by the IRC, per RECIST v1.1) will be the primary endpoint.</td>
</tr>
<tr>
<td>Secondary Endpoints:</td>
</tr>
<tr>
<td>1. Safety profile of orally administered TAK-788</td>
</tr>
<tr>
<td>2. 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</td>
</tr>
</tbody>
</table>
Part 3: Extension Cohort

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
5. PFS, as assessed by the IRC and the investigator
6. OS
7. Patient-reported symptoms (particular core symptoms of lung cancer), functioning, and HRQoL with the EORTC QLQ-C30 and QLQ LC13

Safety Endpoints:
1. Adverse events (AEs)
2. Laboratory values
3. Vital signs
4. Physical examination findings

Exploratory Endpoints:  

state after multiple oral doses

3. Efficacy assessments including: confirmed ORR as assessed by IRC, per RECIST v1.1 (except Expansion Cohort 6); best overall response, best target lesion response, duration of response, DCR, time to response, and PFS, as assessed by the investigator and IRC; and OS
   a. For Expansion Cohort 3, additional efficacy assessments include: intracranial duration of response (iDOR) and intracranial PFS (iPFS)
   b. For Expansion Cohort 6, secondary efficacy assessments will include confirmed ORR as assessed by the investigator, per RECIST v1.1.
**Inclusion Criteria**

**General Inclusion Criteria (all cohorts: dose escalation, expansion, and extension)**

All patients must meet all of the following general inclusion criteria for study entry.

1. Have histologically or cytologically confirmed locally advanced (and not a candidate for definitive therapy) or metastatic disease (Stage IIIB or IV). For all cohorts except Expansion Cohort 7, the locally advanced or metastatic disease is NSCLC. For Expansion Cohort 7, the locally advanced or metastatic disease is any solid tumor other than NSCLC.

2. Must have sufficient tumor tissue available for analysis (see Laboratory Manual for specific requirements). For patients in the expansion cohorts and in the extension cohort, tumor tissue obtained after progression on the most recent prior therapy is preferred.

3. Must have measurable disease by RECIST v1.1 (Appendix B).

4. Male or female adult patients (aged 18 years or older, or as defined per local regulations).

5. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1 (Appendix A).

6. Minimum life expectancy of 3 months or more.

7. Adequate renal and hepatic function as defined by the following criteria:
   - a. Total serum bilirubin $\leq 1.5 \times$ upper limit of normal (ULN) ($\leq 3.0 \times$ ULN for patients with Gilbert syndrome or if liver function abnormalities are due to underlying malignancy);
   - b. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq 2.5 \times$ ULN (or $\leq 5 \times$ ULN if liver function abnormalities are due to underlying malignancy);
   - c. Estimated creatinine clearance $\geq 30$ mL/min (calculated by using the Cockcroft-Gault equation);
   - d. Serum albumin $\geq 2$ g/dL;
   - e. Serum lipase $\leq 1.5 \times$ ULN; and
   - f. Serum amylase $\leq 1.5 \times$ ULN unless the increased serum amylase is due to salivary isoenzymes.

8. Adequate bone marrow function as defined by the following criteria:
   - a. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L;
   - b. Platelet count $\geq 75 \times 10^9$/L; and
   - c. Hemoglobin $\geq 9.0$ g/dL.

9. Normal QT interval on screening electrocardiogram (ECG), defined as QTcF of $\leq 450$ ms in males and $\leq 470$ ms in females.

10. All toxicities from prior therapy have resolved to $\leq$ Grade 1 according to the National Cancer Institute Common Terminology Criteria for Adverse Events.
(NCI CTCAE v5.0 [18]), 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.

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

Male patients, even if surgically sterilized (ie, status postvasectomy), who:
   - Agree to practice effective barrier contraception during the entire study treatment period and through 30 days after the last dose of study drug, OR
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

12. Signed and dated informed consent indicating that the patient has been informed of all pertinent aspects of the study.

13. Willingness and ability to comply with scheduled visits and study procedures.

Cohort-Specific Inclusion Criteria
In addition to the general inclusion criteria above, patients must also meet all criteria for the cohort in which their entry is proposed.

Part 1: Dose escalation cohorts
   - Refractory to standard available therapies.

Part 2: Expansion cohorts
Expansion Cohort 1: NSCLC patients with EGFR exon 20 activating insertions, who have either not received or not shown an objective response to an EGFR TKI, and who have no active, measurable CNS metastases
   1. Have a documented EGFR in-frame exon 20 insertion by a local test, including A763_Y764insFQEA, V769_D770insASV, D770_N771insNPG, D770_N771insSVD, H773_V774insNPH, or any other in-frame exon 20 insertion mutation. The EGFR exon 20 insertion mutation can be either alone or in combination with other EGFR or HER2 mutations.
   2. Previously treated with one or more regimens of systemic therapy for locally advanced or metastatic disease.
   3. Prior treatment with an EGFR TKI is allowed unless the patient had an objective response and subsequent progression as assessed by the investigator or treating physician during treatment with that prior TKI.

Expansion Cohort 2: NSCLC patients with HER2 exon 20 activating insertions or point mutations and no active, measurable CNS metastases
1. Have one of the following documented by a local test:
   a. A HER2 exon 20 insertion including A775_G776insYVMA, G776_V777insVC, or P780_Y781insGSP, or any other in-frame exon 20 insertion mutation.
   b. An activating point mutation in HER2 including, but not limited to, L755S, G776V, and V777L.
   The HER2 exon 20 insertion mutation or point mutation can be either alone or in combination with other EGFR mutations except EGFR exon 20 insertion mutations.
2. Previously treated with one or more regimens of systemic therapy for locally advanced or metastatic disease.
3. Prior treatment with a pan-HER TKI (eg, afatinib, neratinib, or dacomitinib) is allowed unless the patient had an objective response and subsequent progression as assessed by the investigator or treating physician during treatment with that prior TKI.

Expansion Cohort 3: NSCLC patients with EGFR exon 20 activating insertions or HER2 exon 20 activating insertions or point mutations and active, measurable CNS metastases

1. Have one of the following documented by a local test:
   b. A HER2 exon 20 insertion: A775_G776insYVMA, G776_V777insVC, P780_Y781insGSP, or any other in-frame exon 20 insertion mutation.
   c. An activating point mutation in HER2 including, but not limited to, L755S, G776V, and V777L.
   The above mutations can be either alone or in combination with other EGFR mutations.

2. Previously treated with one or more regimen of systemic therapy for locally advanced or metastatic disease.
3. For patients with an EGFR exon 20 insertion: prior treatment with an EGFR TKI is allowed unless the patient had an objective response and subsequent progression as assessed by the investigator or treating physician during treatment with that prior TKI.
4. For patients with a HER2 exon 20 insertion or HER2 activating point mutation: prior treatment with a pan-HER TKI (eg, afatinib, neratinib, or dacomitinib) is allowed unless the patient had an objective response and subsequent progression as assessed by the investigator or treating physician during treatment with that prior TKI.
5. Have either previously untreated intracranial CNS metastases or previously treated intracranial CNS metastases with radiologically documented new or progressing CNS lesions.
6. Have at least one target (ie, measurable) intracranial CNS lesion (≥10 mm in longest diameter by contrast enhanced magnetic resonance imaging [MRI]). Lesions previously treated by stereotactic radiosurgery (SRS) or surgical resection should not be included as a target lesion. Lesions previously treated with whole brain radiation therapy (WBRT) may be included as a target lesion if (1) the last administration of WBRT was >3 months prior to the first dose of TAK-788 and (2) unequivocal radiological progression of the lesion has been observed.

Expansion Cohort 4: NSCLC patients with other targets against which TAK-788 is
active, without active CNS metastases

1. Have one of the following documented by a local test: an activating mutation in EGFR including exon 19 deletions or exon 21 L858R substitution (with or without T790M), or an uncommon activating mutation other than exon 20 insertion including, but not limited to, G719X (where X is any other amino acid), S768I, L861Q, or L861R.
2. Treatment naïve for locally advanced or metastatic disease or previously treated with one or more regimens of systemic therapy for locally advanced or metastatic disease.

Expansion Cohort 5: NSCLC patients with EGFR exon 20 activating insertions, who have previously shown an objective response to or SD with an EGFR TKI and subsequently progressed, without active CNS metastases

1. Have a documented EGFR in-frame exon 20 insertion by a local test, including A763_Y764insFQEA, V769_D770insASV, D770_N771insNPG, D770_N771insSVD, H773_V774insNPH, or any other in-frame exon 20 insertion mutation. The EGFR exon 20 insertion mutation can be either alone or in combination with other EGFR or HER2 mutations.
2. Previously treated with one or more regimens of systemic therapy for locally advanced or metastatic disease.
3. Previously showed an objective response to an EGFR TKI or SD for at least 6 months with an EGFR TKI, then subsequently progressed as assessed by the investigator or treating physician.

Expansion Cohort 6: NSCLC patients with EGFR exon 20 activating insertions, who have not received prior systemic anticancer treatment for locally advanced or metastatic disease, without active CNS metastases

1. Have a documented EGFR in-frame exon 20 insertion by a local test, including A763_Y764insFQEA, V769_D770insASV, D770_N771insNPG, D770_N771insSVD, H773_V774insNPH, or any other in-frame exon 20 insertion mutation. The EGFR exon 20 insertion mutation can be either alone or in combination with other EGFR or HER2 mutations.
2. No prior systemic treatment for locally advanced or metastatic disease (with the exception below):
   Prior adjuvant chemotherapy for Stage I to III or combined modality chemotherapy/radiation for locally advanced disease is allowed if completed >12 months prior to the first dose of TAK-788.

Expansion Cohort 7: Patients with solid tumors other than NSCLC with EGFR/HER2 mutations against which TAK-788 is active, without active CNS metastases

1. Have a locally advanced or metastatic solid tumor that is not NSCLC, including, but not limited to, bladder/urinary tract cancer, breast cancer, gastric/esophageal cancer, biliary tract cancer, and head and neck cancer.
2. Is refractory to standard therapy.
3. Have a target against which TAK-788 is active, documented by a local test, including, but not limited to, the following:
   a. An activating mutation in EGFR including exon 20 insertions, exon 19 deletions or exon 21 L858R substitution (with or without T790M), or an uncommon activating mutation including G719X (where X is any other amino acid), S768I, L861Q, or L861R.
   b. A HER2 exon 20 insertion: A775_G776insYVMA, G776_V777insVC, P780_Y781insGSP, or any other in-frame exon 20 insertion mutation.
   c. An activating point mutation in HER2 including, but not limited to, L755S, G776V, and V777L.
## Part 3: Extension cohort

1. Have 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) assessed by a Clinical Laboratory Improvements Amendment (CLIA)-certified (United States [US] sites) or an accredited (outside of the US) local laboratory and sufficient tumor tissue available for central analysis (see Laboratory Manual). The EGFR exon 20 insertion mutation can be either alone or in combination with other EGFR or HER2 mutations. Note: central confirmation is not required for enrollment.

2. Must have received at least 1 prior line of therapy for locally advanced or metastatic disease and no more than 2 regimens of systemic anticancer chemotherapies for locally advanced or metastatic disease.
   - Note: A systemic anticancer chemotherapy regimen will be counted if it is administered over at least 1 cycle. A new antineoplastic chemotherapy used as maintenance therapy will be counted as a new regimen. Neoadjuvant or adjuvant systemic anticancer chemotherapy will be counted as a prior regimen if completion of the (neo)adjuvant therapy occurred <12 months prior to enrollment.
   - Prior treatment with an EGFR TKI is allowed unless the patient had an objective response and subsequent progression as assessed by the investigator or treating physician during treatment with that prior TKI.

### Exclusion Criteria

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

1. Previously received TAK-788.

2. Received small-molecule anticancer therapy (including cytotoxic chemotherapy and investigational agents) ≤14 days prior to first dose of TAK-788 (except for reversible EGFR TKIs [ie, erlotinib or gefitinib], which are allowed up to 7 days prior to the first dose of TAK-788).

3. Received antineoplastic monoclonal antibodies including immunotherapy within 28 days of the first dose of TAK-788.

4. 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. Note: This exclusion criterion does not apply to Expansion Cohort 7.

5. Received radiotherapy ≤14 days prior to the first dose of TAK-788 or has not recovered from radiotherapy-related toxicities. Palliative radiation administered outside the chest and brain, SRS, and stereotactic body radiotherapy are allowed up to 7 days prior to the first dose.

6. 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 C).

7. 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.

8. Part 1 (dose escalation) and Expansion Cohorts 1 to 3 of Part 2 (expansion
phase) only:
Have symptomatic CNS metastases at screening or asymptomatic disease requiring corticosteroids to control symptoms within 7 days prior to the first dose of TAK-788.

Part 3 (extension cohort) and Expansion Cohorts 4 to 7 of Part 2 (expansion phase) only:
Have known active brain metastases (have either previously untreated intracranial CNS metastases or previously treated intracranial CNS metastases with radiologically documented new or progressing CNS lesions). Brain metastases are allowed if they have been treated with surgery and/or radiation and have been stable without requiring corticosteroids to control symptoms within 7 days before the first dose of TAK-788, and have no evidence of new or enlarging brain metastases.

9. Have current spinal cord compression (symptomatic or asymptomatic and detected by radiographic imaging) or leptomeningeal disease (symptomatic or asymptomatic).

10. Have significant, uncontrolled, or active cardiovascular disease, including, but not restricted to:
   a. Myocardial infarction (MI) within 6 months prior to the first dose of study drug;
   b. Unstable angina within 6 months prior to first dose;
   c. Congestive heart failure (CHF) within 6 months prior to first dose;
   d. History of clinically significant (as determined by the treating physician) atrial arrhythmia;
   e. Any history of ventricular arrhythmia; or
   f. Cerebrovascular accident or transient ischemic attack within 6 months prior to first dose.

11. Have a known history of uncontrolled hypertension. Patients with hypertension should be under treatment on study entry to control blood pressure.

12. Have prolonged QTcF interval, or being treated with medications known to be associated with the development of Torsades de Pointes (Appendix D).

13. (Parts 1 and 2 [dose escalation and expansion cohorts] only) Have an ongoing or active infection including, but not limited to, the requirement for intravenous (IV) antibiotics, or a known history of human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV). Testing is not required in the absence of history.

   (Part 3 [extension cohort] only) Have an ongoing or active infection including, but not limited to, the requirement for IV antibiotics, or a known history of HIV. Testing is not required in the absence of history.

   (Part 3 [extension cohort] only) Hepatitis B surface antigen (HBsAg) positive patients are allowed to enroll if HBV DNA is below 1000 copies/mL in the plasma. Patients who are positive for anti-HCV antibody (HCVAb) can be enrolled but must not have detectable HCV RNA in the plasma.

14. Currently have or have a history of interstitial lung disease, radiation pneumonitis that required steroid treatment, or drug-related pneumonitis.

15. Female patients who are lactating and breastfeeding or have a positive urine or
<table>
<thead>
<tr>
<th>Approximate Number of Patients</th>
<th>Serum pregnancy test during the screening period. Note: Female patients who are lactating will be eligible if they discontinue breastfeeding.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>16. Have gastrointestinal illness or disorder that could affect oral absorption of TAK-788.</td>
</tr>
<tr>
<td></td>
<td>17. 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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Approximate Number of Patients</th>
<th>Approximately 311 to 341 patients total in the study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. Dose escalation cohort</td>
</tr>
<tr>
<td></td>
<td>a. Approximately 5 to 10 dose levels = approximately 50 to 80 patients total</td>
</tr>
<tr>
<td></td>
<td>2. Expansion cohorts</td>
</tr>
<tr>
<td></td>
<td>a. Cohort 1 = approximately 20 patients</td>
</tr>
<tr>
<td></td>
<td>b. Cohort 2 = approximately 20 patients</td>
</tr>
<tr>
<td></td>
<td>c. Cohort 3 = approximately 20 patients</td>
</tr>
<tr>
<td></td>
<td>d. Cohort 4 = approximately 30 patients</td>
</tr>
<tr>
<td></td>
<td>Note: Cohort 4 will enroll at least 20 patients with an uncommon activating mutation either alone or in combination with other EGFR mutations except exon 20 insertion mutations.</td>
</tr>
<tr>
<td></td>
<td>e. Cohort 5 = approximately 20 patients</td>
</tr>
<tr>
<td></td>
<td>f. Cohort 6 = approximately 30 patients</td>
</tr>
<tr>
<td></td>
<td>g. Cohort 7 = approximately 30 patients with at least 20 patients with a HER2 activating mutation, either alone or in combination with other EGFR mutations.</td>
</tr>
<tr>
<td></td>
<td>3. Extension cohort</td>
</tr>
<tr>
<td></td>
<td>a. Approximately 91 patients</td>
</tr>
</tbody>
</table>

| Approximate Duration of Patient Participation | After a 2- to 3-week screening period, patients will 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. Patients will have an assessment at 30 days after treatment discontinuation. OS will also be measured at least every 3 months after treatment discontinuation until at least 3 years after the last patient is enrolled into the study. |

| Approximate Duration of Study | The total estimated duration of the dose escalation and expansion components of the study is approximately 6 years, including 36 months to accrue patients and 3 years for treatment and follow-up after the last patient enrolls. The total estimated duration of the extension cohort component of the study is approximately 4 years, including approximately 13 months to accrue patients and 3 years for treatment and follow-up of the last patient. Patients who are still on study at 3 years will be allowed to receive study drug beyond 3 years, either until disease progression or until they discontinue treatment for other reasons. Patients who are still receiving study drug 3 years after the last patient enrolls may be eligible to receive posttrial access to TAK-788. |
| Approximate Number of Study Centers | Approximately 7 to 14 centers in the US will enroll patients during the dose escalation phase. Approximately 7 to 20 additional centers in the US will be activated for enrollment of the expansion cohorts. Approximately 100 centers in North America, Europe, and Asia will enroll patients in the extension cohort. |
| Dosage and Administration | **Part 1: Dose Escalation**
The dose escalation phase of the proposed phase 1/2 trial will employ sequential, dose-escalation of oral TAK-788 using a standard 3+3 design, starting at a dose of 5 mg administered orally QD, and increasing in increments until the MTD is identified. Initially, an increase of up to 100% over the previous dose level cohort will be employed until a Grade 2 drug-related toxicity of diarrhea or skin rash occurs, based on consideration of expected class effects for EGFR TKIs, or other DLTs are identified. Further dose escalation will involve increments of no more than 50% of the previous dose, depending on safety findings. Alternative dosing regimens may be administered based on PK findings for the initial patients. Should a modification of dosing levels be required, the dose escalation scheme will be altered by interpolating non-QD schedules into the initial escalation scheme. Each dose escalation cohort will have a minimum of 3 patients enrolled and followed for 28 days. Increasing to the next dose level will depend on the safety findings of the previous cohorts. Expansion of a cohort from 3 to 6 patients will occur if 1 of 3 patients experiences a DLT at a given dose. Expansion of the cohort size may also occur at any dose to confirm safety, efficacy, and PK observations. Intermediate doses between the MTD and the next lower dose may be explored. Administration schedules for single or multiple dosing of TAK-788 in a given period or alternative schedules may be explored depending on PK findings and safety and tolerability data in continuous dosing cohorts. Intra-patient dose escalation will be allowed according to the following scheme. All patients will have the option to increase dose while on the study if the following conditions are met: 1) the patient tolerated his/her starting dose without a DLT, 2) the Cycle 2 PK samples have been drawn per protocol, and 3) the proposed next dose level has been evaluated and shown not to exceed the MTD. **Parts 2 and 3: Expansion and Extension Cohorts**
The Phase 2 expansion and extension cohorts will receive TAK-788 at the RP2D of 160 mg QD. Patients will continue to be treated with TAK-788 until they experience 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. |
2. Use of any other investigational drug or device;
3. 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 (see Appendix D), should be avoided but are not prohibited;
4. Herbal preparations or related over-the-counter preparations containing herbal ingredients, or other folk remedies;
5. Grapefruit or grapefruit-containing products, pomegranate, pomelo, or star fruit juice containing products, and Seville oranges;
6. Extensive surgery requiring in-patient care (patients may have an interruption in therapy for 2 weeks should emergency surgery be required);
7. Medications that are moderate inducers or inhibitors or strong inducers or inhibitors of the CYP3A family of Cytochromes P450 (see Appendix C), with the exception of nonsystemic use (e.g., topical).
8. Any illicit substance. Note: Medical use of cannabis is allowed, if it is legal where the patient resides and no alternative treatment is available, on the basis of case-by-case review and agreement by the medical monitor.

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 and other pregnane X receptor–inducible enzymes (e.g., CYP2C9, CYP2C19) and transporters (e.g., P glycoprotein), including hormonal contraceptives, can result in decreased concentrations and loss of efficacy of these coadministered drugs.

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:

1. Medications that are CYP3A substrates and which have narrow therapeutic index including alfentanil, cyclosporine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus, and all statins;
2. CYP2C8 sensitive substrates, including repaglinide, dasabuvir and amodiaquine;
3. Warfarin, a CYP2C9 sensitive substrate;
4. S-mephenytoin, a CYP2C19 sensitive substrate.

Safety Evaluation

Safety assessments will include physical and laboratory examinations, vital signs, and ECGs. AEs will be graded according to the National Cancer Institute (of the United States) Common Terminology Criteria for Adverse Events (NCI CTCAE v4.0 before Amendment 3 and v5.0 after Amendment 3). Periodic meetings with study investigators will be held to assess safety data during the dose escalation phase.

All patients receiving at least 1 dose of TAK-788 will be considered evaluable for safety. The AE incidence rates, as well as the frequency of overall toxicity, categorized by toxicity Grades (severity), will be described. Listings of laboratory test results will also be generated, and descriptive statistics summarizing the changes in laboratory tests over time will be presented.

**Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose (RP2D)**

The MTD is defined as the highest dose at which ≤1 of 6 evaluable patients experience a 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. The cohort may be expanded to better define the safety profile for confirmation of the MTD.
The maximum administered dose in the trial will likely exceed the MTD. 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.

**Dose-Limiting Toxicities (DLTs)**

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 v4.0 prior to Amendment 3 and by NCI CTCAE v5.0 following Amendment 3, if needed. DLTs are defined by the following:

Non-hematologic toxicities

i. Any ≥ Grade 3 non-hematologic toxicity, with the exception of self-limiting or medically controllable toxicities (e.g., nausea, vomiting, fatigue, electrolyte disturbances, hypersensitivity reactions) lasting < 3 days, and excluding alopecia.

Hematologic toxicities

i. Febrile neutropenia not related to underlying disease (fever, >101°F [>38.3°C]; absolute neutrophil count [ANC] < 0.5 × 10^9/L);

ii. Prolonged Grade 4 neutropenia (≥ 7 days);

iii. Neutropenic infection: ≥ Grade 3 neutropenia with ≥ Grade 3 infection;

iv. Thrombocytopenia ≥ Grade 3 with bleeding or Grade 4 without bleeding lasting ≥ 7 days

Missed ≥ 25% of planned doses of TAK-788 over 28 days due to treatment-related AEs in the first cycle.

**QT Interval Evaluation**

The following ECG assessments will be required for the dose escalation and expansion cohorts: triplicate ECGs at baseline on Cycle 1, Day 1 before the first administration of TAK-788, and triplicate ECGs on Cycle 2, Day 1 (Day 29) prior to administration of the Cycle 2, Day 1 dose; and at 1, 2, 4, and 6 hours after dosing of TAK-788 on Cycle 2, Day 1. Adjustments to the timing of triplicate ECGs on Cycle 2, Day 1 may be made based on the PK findings in the dose escalation phase. The ECG performed at screening and ECGs done after completion of Cycle 2 may be a single ECG. ECGs will be recorded electronically and will be evaluated centrally in Parts 1 and 2 of the study (dose escalation and expansion phases).

For the Part 3 extension cohort, single ECGs only will be performed at pre-specified time points (see Schedule of Events) and will be evaluated centrally for sites in the US and locally for sites outside of the US.

**Pharmacokinetic Evaluation**

Blood samples will be collected at pre-specified time points (see Schedule of Events) to assess the plasma concentrations of TAK-788 and active metabolites (AP32960 and AP32914) following a single dose and multiple doses (steady state) of TAK-788 in the dose escalation cohorts. PK parameters, such as time of maximum concentration, maximum concentration, area under the concentration-time curve, clearance, volume of distribution, terminal half-life, and accumulation ratio, will be estimated where possible.

PK evaluation will also be performed for the expansion cohorts to obtain cohort-specific PK at the recommended dose established in the dose escalation phase of the trial. PK sampling time points are initially planned to be the same as the sampling time points in the dose escalation phase; however, adjustments may be made based on the PK findings in the dose escalation phase.
Sparse blood samples will also be collected at pre-specified time points in the extension cohort for population PK and exposure-response analyses.

<table>
<thead>
<tr>
<th>Efficacy Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the expansion and extension cohorts, anti-tumor activity will primarily be assessed by confirmed ORR using RECIST v1.1 (as determined by the investigator for the expansion cohorts and the IRC for the extension cohort), except for Expansion Cohort 3, in which anti-tumor activity will primarily be assessed by iORR (as determined by the IRC) and Expansion Cohort 6, in which anti-tumor activity will primarily be assessed by confirmed ORR per RECIST v1.1 (as determined by the IRC). Secondary measures of efficacy will include: best target lesion response, duration of response, DCR, time to response, and PFS. OS will also be measured.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exploratory Biomarker Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>The mutation status of EGFR, HER2, and other genes implicated in tumor biology, drug metabolism, and/or immunoprofiling will be determined through analyses of tumor tissue.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Statistical Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parts 1 and 2: Dose Escalation and Expansion Cohorts</strong></td>
</tr>
<tr>
<td>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. For the expansion cohorts, estimates of clinical activity, including response rate, duration of response, DCR, time to response, PFS, and best target lesion response, will be determined. Clinical activity in patients with intracranial disease will be analyzed separately. For Expansion Cohort 6, two-sided exact 95% binomial confidence intervals (CIs) will be computed for the primary endpoint and all binary secondary endpoints, including confirmed ORR as assessed by the investigator and DCR as assessed by the IRC and the investigator.</td>
</tr>
<tr>
<td><strong>Part 3: Extension Cohort</strong></td>
</tr>
<tr>
<td>All patients enrolled in the extension cohort who receive at least 1 dose of TAK-788 (full analysis set) will be included in the primary analyses of efficacy and safety.</td>
</tr>
<tr>
<td>The primary analysis of the primary endpoint, confirmed ORR as assessed by the IRC, will be performed in the full analysis set when all ongoing patients have completed their Cycle 6 disease assessment. A futility analysis will be planned for the primary endpoint when approximately 20 patients have completed their Cycle 4 disease assessment. Two-sided exact 95% binomial CIs will be computed for all binary secondary endpoints, including confirmed ORR as assessed by the investigator and DCR as assessed by the IRC and the investigator. Kaplan-Meier methods, including medians and CIs, will be used to estimate PFS as assessed by the IRC and the investigator, duration of response as assessed by the IRC and the investigator, and OS. Descriptive statistics will be used to summarize time to response in responders and time on treatment. Patient-reported outcome assessments will be assessed at each cycle using descriptive summary statistics.</td>
</tr>
<tr>
<td><strong>Pharmacokinetic Analysis</strong></td>
</tr>
<tr>
<td>The PK parameters for TAK-788 and its active metabolites,</td>
</tr>
</tbody>
</table>

**Note:** The content above is a sample of the document's content, focused on specific sections for clarity and brevity. The complete document includes additional details and sections not shown here.
Following a single oral dose in the dose escalation and expansion cohorts:

- Maximum observed concentration ($C_{\text{max}}$); time of first occurrence of $C_{\text{max}}$ ($t_{\text{max}}$); and area under the concentration-time curve from time zero to 24 hours ($\text{AUC}_{24}$) and from time zero to time $t$ ($\text{AUC}_t$). Dose proportionality for $C_{\text{max}}$ and AUC will be assessed.

Following multiple oral doses (steady state) in the dose escalation and expansion cohorts:

- Maximum observed concentration during a dosing interval, at steady state ($C_{\text{max,ss}}$); time of first occurrence of $C_{\text{max,ss}}$ ($t_{\text{max,ss}}$); $\text{AUC}_{24}$; $\text{AUC}_t$; apparent clearance at steady state ($\text{CL/F}_{\text{ss}}$); volume of distribution at steady state ($V_{\text{d,F}_{\text{ss}}}$); accumulation ratio based on the area under the concentration-time curve during a dosing interval ($R_{\text{AUC,ss}}$); accumulation ratio based on $C_{\text{max}}$ ($R_{\text{AUC,C_{max}}}$); and effective half-life ($t_{\frac{1}{2}\text{eff}}$). Dose proportionality for $C_{\text{max}}$ and AUC will be assessed.

### QTc Analysis

For Parts 1 and 2 (dose escalation and expansion cohorts), descriptive statistics of maximum QTcF and change from baseline will be calculated following the ICH-E14 guidelines: the proportion of treated patients with at least 1 on-drug QTcF value $>450$ ms, $480$ ms, and $500$ ms; the proportion of treated patients with a maximum change in QTcF from baseline $>30$ ms and $>60$ ms. The Fridericia correction (QTcF) will be used throughout. The PK and ECG data collected in this study will contribute to analysis of concentration-effect (such as QTc change from baseline) relationships using linear mixed effects models.

### Rationale for Number of Patients

#### Parts 1 and 2: Dose Escalation and Expansion Cohorts

The purpose of the dose escalation and expansion phases of this phase 1/2 trial is to determine the RP2D and MTD, as well as evaluate the safety, tolerability, and anti-tumor activity of oral TAK-788 in patients with advanced NSCLC and other solid tumors. The sample size is determined based on clinical rather than statistical considerations. The number of patients in this trial is consistent with phase 1 dose finding studies; the histologically and molecularly defined expansion cohorts will facilitate obtaining estimates of clinical activity. With this design, the estimate of the rate of DLT at the MTD is in the range of 0.17 to 0.26. The estimate of the rate of DLT at the highest dose, which is 1 step above the MTD, is 0.33 [19].

#### Part 3: Extension Cohort

The purpose of the extension cohort in the phase 2 part of this study is to determine the confirmed ORR of orally administered TAK-788 at 160 mg QD in patients with NSCLC with EGFR exon 20 insertion mutations. Approximately 91 patients with NSCLC with tumors harboring EGFR exon 20 insertion mutations on the basis of a local test will be enrolled to include approximately 73 patients with centrally confirmed EGFR exon 20 insertion mutations, assuming a 20% discrepancy between the documented mutation status by local testing results and central testing using an analytically validated central test.
## TABLE OF CONTENTS

1. **PROTOCOL REVISION HISTORY** ................................................................. 1

2. **DISCLOSURE STATEMENT** .................................................................... 2

3. **SIGNATURE PAGES AND PROTOCOL AMENDMENT SUMMARY OF CHANGES** ...................................................... 8

4. **PROTOCOL SYNOPSIS** ......................................................................... 8

5. **TABLE OF CONTENTS** ......................................................................... 25

6. **LIST OF ABBREVIATIONS** .................................................................. 30

7. **DEFINITIONS OF TERMS** ................................................................... 33

8. **INTRODUCTION** ...................................................................................... 35

   8.1 Background ............................................................................................ 35

       8.1.1 Study Drug and Rationale ................................................................. 36

       8.1.2 Rationale for RP2D ....................................................................... 37

       8.1.3 Benefit-Risk .................................................................................. 39

9. **STUDY OBJECTIVES** ............................................................................ 40

10. **INVESTIGATIONAL PLAN** .................................................................... 41

    10.1 Overall Study Design and Plan .............................................................. 41

    10.2 Randomization and Blinding ................................................................. 44

11. **SELECTION OF STUDY POPULATION** .............................................. 44

    11.1 Inclusion Criteria ................................................................................. 44

        11.1.1 General Inclusion Criteria (All Cohorts: Dose Escalation, Expansion, and Extension) ........................................ 44

        11.1.2 Cohort-Specific Inclusion Criteria .............................................. 45

    11.2 Exclusion Criteria ................................................................................ 49

12. **STUDY PROCEDURES** ......................................................................... 51

    12.1 Study Procedure Descriptions .............................................................. 51

        12.1.1 Schedule of Events ....................................................................... 58

    12.2 Screening Period .................................................................................. 63

    12.3 Screen Failures ..................................................................................... 63

    12.4 Treatment Through 30 Days after Last Dose of Study Drug ............... 63

    12.5 End of Treatment or Early Termination .............................................. 63

    12.6 30 Days After Last Dose ...................................................................... 63

    12.7 Follow-up Period Procedures ............................................................... 63

    12.8 Study Duration ...................................................................................... 64

        12.8.1 Study Completion Definition ......................................................... 64

        12.8.2 Approximate Duration of Patient Participation ......................... 64

        12.8.3 Approximate Duration of Study ................................................... 64

        12.8.4 Posttrial Access ........................................................................... 64

    12.9 Patient Discontinuation ....................................................................... 65

    12.10 Study or Site Termination ................................................................. 66

Amendment 6 02 September 2020
12.11 Sample Collection, Storage, and Shipping ............................................. 66

13 Efficacy and Safety Assessments ................................................................. 66
13.1 Efficacy Assessments ............................................................................... 66
13.2 Safety Assessments .................................................................................. 66
13.3 Pharmacokinetic Assessments .................................................................. 67
13.4 CCT .......................................................................................................... 67
13.5 Patient-Reported Outcome Assessments (for Part 3 [Extension Cohort] Only) ................................................. 67

14 Study Treatment .......................................................................................... 68
14.1 Study Drug .................................................................................................. 68
14.2 Selection of the Starting Dose ................................................................... 69
14.2.1 Treatment Administration ...................................................................... 69
14.2.2 Part 1: Dose Escalation .......................................................................... 69
  14.2.2.1 Intra-patient Dose Escalation ......................................................... 71
  14.2.2.2 Maximum Tolerated Dose (MTD) .................................................. 71
  14.2.2.3 Dose-Limiting Toxicities (DLTs) .................................................... 71
14.2.3 Management of Adverse Drug Reactions ............................................ 72
  14.2.4 Dose Modification(s) ........................................................................... 72
     14.2.4.1 Management of Selected Treatment-Related Adverse Events ........................................................................ 73
     14.2.4.2 Dose Re-escalation ...................................................................... 74
  14.2.5 Initiation of Part 2 (Expansion Phase) and Part 3 (Extension Cohort) Enrollment .................................................. 74
14.3 Prior and Concomitant Treatment(s)/Therapy ......................................... 74
14.4 Prohibited Treatment(s)/Therapy .............................................................. 74
14.5 Potential Drug Interactions ....................................................................... 75
14.6 Treatment Compliance .............................................................................. 76
14.7 Treatment(s) Supply ................................................................................ 76
  14.7.1 Formulation, Packaging, and Labeling .............................................. 77
  14.7.2 Treatment(s) Storage, Dispensing, and Accountability ....................... 77
     14.7.2.1 Disposition of Unused Supplies .................................................. 77
     14.7.2.2 Inventory of Unused Supplies .................................................... 77

15 Adverse Event Reporting ............................................................................ 78
15.1 Adverse Events .......................................................................................... 78
  15.1.1 Adverse Event Definition ..................................................................... 78
  15.1.2 Performing Adverse Events Assessments ......................................... 79
  15.1.3 Reporting Period .................................................................................. 79
  15.1.4 Adverse Event Severity ...................................................................... 79
  15.1.5 Causality ............................................................................................. 80
  15.1.6 Expectedness ....................................................................................... 81
  15.2 Serious Adverse Events .......................................................................... 81
     15.2.1 Serious Adverse Event Definition .................................................... 81
        15.2.1.1 Progression of the Malignancy Under Study .............................. 82
        15.2.1.2 Hospitalizations ....................................................................... 82
     15.2.2 Reporting Serious Adverse Events ................................................. 83
18.4 Study Committees........................................................................................98
  18.4.1 Parts 2 and 3: Independent Review Committee.................................98
  18.4.2 Part 3: Data Monitoring Committee (for Extension Cohort)..............99
  18.4.3 Part 3: Study Steering Committee (for Extension Cohort)..............99

19 DATA HANDLING AND RECORD KEEPING...................................................99
  19.1 Case Report Forms and Study Records......................................................99
  19.2 Access to Source Documentation .................................................................99
  19.3 Retention of Data.......................................................................................100
  19.4 Termination of Study ................................................................................100

20 FINANCING AND INSURANCE ........................................................................100

21 PUBLICATION AND DISCLOSURE POLICY ........................................... 101

22 REFERENCES .....................................................................................................103

23 APPENDICES .......................................................................................................106
TABLE OF TABLES
Table 1 Schedule of Events (Parts 1 and 2: Dose Escalation and Expansion Cohorts) .....59
Table 2 Schedule of Events (Part 3: Extension Cohort) ..........................................................61
Table 3 Dose Modifications..................................................................................................72
Table 4 TAK-788 Dose Reduction Schedule for Parts 2 and 3 (Expansion and Extension
Phases)..................................................................................................................................73
Table 5 Highly Effective Methods of Contraception and Additional Effective (Barrier)
Methods.............................................................................................................................86

TABLE OF FIGURES
Figure 1 Schematic of TAK-788 Phase 1/2 Trial Design – Dose Escalation, Expansion, and
Extension Phases .............................................................................................................43
Figure 2 Schematic of TAK-788 Phase 1/2 Trial Design – Dose Escalation Phase..............70

LIST OF APPENDICES
Appendix A Eastern Cooperative Oncology Group Performance Status .......................107
Appendix B Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1).....108
Appendix C Drugs That Interact With the CYP3A Family of Cytochromes P450........110
Appendix D Drugs With a Risk of Torsades de Pointes ..................................................112
Appendix E Responsibilities of the Investigator .............................................................115
Appendix F Protocol History ............................................................................................117
## 6 LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>adverse event</td>
</tr>
<tr>
<td>ALT</td>
<td>alanine aminotransferase</td>
</tr>
<tr>
<td>ANC</td>
<td>absolute neutrophil count</td>
</tr>
<tr>
<td>AST</td>
<td>aspartate aminotransferase</td>
</tr>
<tr>
<td>AUC</td>
<td>area under the concentration-time curve</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;24&lt;/sub&gt;</td>
<td>area under the concentration-time curve from time zero to 24 hours</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;t&lt;/sub&gt;</td>
<td>area under the concentration-time curve from time zero to time t</td>
</tr>
<tr>
<td>ß-HCG</td>
<td>beta-human chorionic gonadotropin</td>
</tr>
<tr>
<td>BUN</td>
<td>blood urea nitrogen</td>
</tr>
<tr>
<td>CBC</td>
<td>complete blood count</td>
</tr>
<tr>
<td>cDNA</td>
<td>complementary deoxyribonucleic acid</td>
</tr>
<tr>
<td>cGMP</td>
<td>current Good Manufacturing Practice</td>
</tr>
<tr>
<td>CHF</td>
<td>congestive heart failure</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CL/F&lt;sub&gt;ss&lt;/sub&gt;</td>
<td>apparent clearance at steady state</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>maximum observed concentration</td>
</tr>
<tr>
<td>C&lt;sub&gt;max,ss&lt;/sub&gt;</td>
<td>maximum observed concentration during a dosing interval, at steady state</td>
</tr>
<tr>
<td>CML</td>
<td>chronic myeloid leukemia</td>
</tr>
<tr>
<td>CNF</td>
<td>current National Formulary</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>COVID-19</td>
<td>coronavirus disease 2019</td>
</tr>
<tr>
<td>CR</td>
<td>complete response</td>
</tr>
<tr>
<td>CSR</td>
<td>clinical study report</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>CTC</td>
<td>Common Terminology Criteria</td>
</tr>
<tr>
<td>CTC-CAE</td>
<td>Common Terminology Criteria for Adverse Events</td>
</tr>
<tr>
<td>CYP</td>
<td>cytochrome P450</td>
</tr>
<tr>
<td>DCR</td>
<td>disease control rate</td>
</tr>
<tr>
<td>DDI</td>
<td>drug-drug interaction</td>
</tr>
<tr>
<td>DLT</td>
<td>dose-limiting toxicity</td>
</tr>
<tr>
<td>DMC</td>
<td>Data Monitoring Committee</td>
</tr>
<tr>
<td>DTP</td>
<td>direct-to-patient</td>
</tr>
<tr>
<td>EC</td>
<td>Ethics Committee</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>ECOG</td>
<td>Eastern Cooperative Oncology Group</td>
</tr>
<tr>
<td>eConsent</td>
<td>electronic informed consent</td>
</tr>
<tr>
<td>eCRF</td>
<td>electronic case report form</td>
</tr>
<tr>
<td>EGFR</td>
<td>epidermal growth factor receptor</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>EORTC</td>
<td>European Organisation for Research and Treatment of Cancer</td>
</tr>
<tr>
<td>FFPE</td>
<td>Fixed-formalin paraffin-embedded</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration (United States)</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>HBsAg</td>
<td>hepatitis B surface antigen</td>
</tr>
<tr>
<td>HBV</td>
<td>hepatitis B virus</td>
</tr>
<tr>
<td>HCV</td>
<td>hepatitis C virus</td>
</tr>
<tr>
<td>HCVAb</td>
<td>anti-hepatitis C virus antibody</td>
</tr>
<tr>
<td>HER2</td>
<td>human epidermal growth factor 2</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>HNSTD</td>
<td>highest non-severely toxic dose</td>
</tr>
<tr>
<td>HPFB</td>
<td>Canadian Health Products and Food Branch</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Term</td>
</tr>
<tr>
<td>--------------</td>
<td>------</td>
</tr>
<tr>
<td>HRQoL</td>
<td>health-related quality of life</td>
</tr>
<tr>
<td>IC₅₀</td>
<td>50% inhibitory concentration</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use</td>
</tr>
<tr>
<td>ICMJE</td>
<td>International Committee of Medical Journal Editors</td>
</tr>
<tr>
<td>iDOR</td>
<td>duration of intracranial response</td>
</tr>
<tr>
<td>IEC</td>
<td>Independent Ethics Committee</td>
</tr>
<tr>
<td>IND</td>
<td>Investigational New Drug</td>
</tr>
<tr>
<td>iORR</td>
<td>intracranial objective response rate</td>
</tr>
<tr>
<td>iPFS</td>
<td>intracranial progression free survival</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>IRC</td>
<td>Independent Review Committee</td>
</tr>
<tr>
<td>IV</td>
<td>intravenous</td>
</tr>
<tr>
<td>LDH</td>
<td>lactate dehydrogenase</td>
</tr>
<tr>
<td>LP</td>
<td>lumbar puncture</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>MI</td>
<td>myocardial infarction</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>ms</td>
<td>millisecond</td>
</tr>
<tr>
<td>MTD</td>
<td>maximum tolerated dose</td>
</tr>
<tr>
<td>NCI</td>
<td>National Cancer Institute (of the United States)</td>
</tr>
<tr>
<td>NCI CTCAE, vX.0</td>
<td>NCI Common Terminology Criteria for Adverse Events, version X.0</td>
</tr>
<tr>
<td>NE</td>
<td>non-evaluable</td>
</tr>
<tr>
<td>NSCLC</td>
<td>non-small cell lung cancer</td>
</tr>
<tr>
<td>ORR</td>
<td>objective response rate</td>
</tr>
<tr>
<td>OS</td>
<td>overall survival</td>
</tr>
<tr>
<td>PD</td>
<td>progressive disease</td>
</tr>
<tr>
<td>PFS</td>
<td>progression-free survival</td>
</tr>
<tr>
<td>PK</td>
<td>pharmacokinetic(s)</td>
</tr>
<tr>
<td>PR</td>
<td>partial response</td>
</tr>
</tbody>
</table>

**QOL**

<table>
<thead>
<tr>
<th>Term</th>
<th>Property</th>
</tr>
</thead>
<tbody>
<tr>
<td>QD</td>
<td>once daily</td>
</tr>
<tr>
<td>QLQ</td>
<td>Quality of Life Questionnaire</td>
</tr>
<tr>
<td>QLQ-LC13</td>
<td>Quality of Life Questionnaire, lung cancer module</td>
</tr>
<tr>
<td>QT</td>
<td>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</td>
</tr>
<tr>
<td>QTc</td>
<td>heart rate-corrected QT interval (calculated)</td>
</tr>
<tr>
<td>QTcF</td>
<td>QT interval corrected (Fridericia)</td>
</tr>
<tr>
<td>Rac(AUC)</td>
<td>accumulation ratio based on the area under the concentration-time curve during a dosing interval</td>
</tr>
<tr>
<td>Rac(Cmax)</td>
<td>accumulation ratio based on the maximum observed concentration</td>
</tr>
<tr>
<td>RECIST</td>
<td>Response Evaluation Criteria in Solid Tumors</td>
</tr>
<tr>
<td>RP2D</td>
<td>recommended Phase 2 dose</td>
</tr>
<tr>
<td>SAE</td>
<td>serious adverse event</td>
</tr>
<tr>
<td>SD</td>
<td>stable disease</td>
</tr>
<tr>
<td>SGOT</td>
<td>serum glutamic oxaloacetic transaminase</td>
</tr>
<tr>
<td>SGPT</td>
<td>serum glutamic pyruvic transaminase</td>
</tr>
<tr>
<td>SRS</td>
<td>stereotactic radiosurgery</td>
</tr>
<tr>
<td>STD₁₀</td>
<td>dose that is severely toxic to 10% of tested rodents</td>
</tr>
<tr>
<td>SUSAR</td>
<td>suspected unexpected serious adverse reaction</td>
</tr>
<tr>
<td>t½zeff</td>
<td>effective half-life</td>
</tr>
<tr>
<td>TGA</td>
<td>Australian Therapeutic Goods Administration</td>
</tr>
<tr>
<td>TKI</td>
<td>tyrosine kinase inhibitor</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Term</td>
</tr>
<tr>
<td>--------------</td>
<td>------</td>
</tr>
<tr>
<td>$t_{\text{max}}$</td>
<td>time of first occurrence of maximum observed concentration</td>
</tr>
<tr>
<td>$t_{\text{max,ss}}$</td>
<td>time of first occurrence of maximum observed concentration during a dosing interval, at steady state</td>
</tr>
<tr>
<td>UE</td>
<td>unable to evaluate</td>
</tr>
<tr>
<td>ULN</td>
<td>upper limit of normal</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>$V_z/F_{\text{ss}}$</td>
<td>volume of distribution at steady state</td>
</tr>
<tr>
<td>WBRT</td>
<td>whole brain radiation therapy</td>
</tr>
<tr>
<td>WT</td>
<td>wild-type</td>
</tr>
</tbody>
</table>
## DEFINITIONS OF TERMS

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 Days After Last Dose</td>
<td>At 30 Days After Last Dose of study drug, a patient completes all post-treatment discontinuation assessments.</td>
</tr>
<tr>
<td>Clinically Significant</td>
<td>A clinical observation or laboratory result that leads to a new intervention or change in therapy is defined in the context of this study as <em>clinically significant</em>.</td>
</tr>
<tr>
<td>Cycle</td>
<td>For the purposes of this study, a <em>cycle</em> consists of 28 days and is equivalent to a month in the measurement of study endpoints.</td>
</tr>
<tr>
<td>End of Treatment</td>
<td>The <em>end of treatment</em> occurs at the last dose of study drug or when the investigator and patient decide that the patient will receive no further study drug, whichever occurs later.</td>
</tr>
<tr>
<td>End of Study</td>
<td><em>End of study (completion)</em> date is 3 years after the last patient has enrolled, unless stopped earlier due to futility or sponsor decision.</td>
</tr>
<tr>
<td>Enrolled Patient</td>
<td>An <em>enrolled patient</em> is a patient who has signed the informed consent form, completed all screening evaluations, and has been administered the first dose of study drug.</td>
</tr>
<tr>
<td>Ethics Committee</td>
<td>Throughout this document, the term <em>Ethics Committee</em> (EC) refers to all appropriate properly constituted committees or boards recognized by the appropriate regulatory agencies for approving clinical studies. These include independent EC and Institutional Review Boards.</td>
</tr>
<tr>
<td>Evaluable for Efficacy</td>
<td>Any eligible patient who is administered at least one dose of the study drug is considered <em>evaluable for efficacy</em> analyses.</td>
</tr>
<tr>
<td>Evaluable for Safety</td>
<td>Any patient who is administered at least one dose of the study drug is considered <em>evaluable for safety</em> analyses.</td>
</tr>
<tr>
<td>Follow-up Period</td>
<td>The <em>follow-up period</em> for survival begins at the end of treatment and continues until patient contact discontinues.</td>
</tr>
<tr>
<td>Institutional Review Board</td>
<td>Throughout this document, the term <em>Institutional Review Board</em> (IRB) refers to all appropriate properly constituted committees or boards recognized by the appropriate regulatory agencies for approving clinical studies. These include independent ECs and IRBs.</td>
</tr>
<tr>
<td>Patient</td>
<td>Throughout this document, the term <em>patient</em> refers to a patient in this clinical research study.</td>
</tr>
<tr>
<td>QTcF</td>
<td>QT corrected (Fridericia) Calculation Formula: QTcF=QT/(RR)^{1/3}, where RR=the interval from the onset of one QRS complex to the onset of the next QRS complex, measured in seconds.</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>----------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Regulation</td>
<td>Throughout this document, the term <em>regulation</em> refers to all appropriate regulations, laws, and guidelines. This study will be conducted according to all appropriate regulations. The regulations may be international, national, or local, and may include but not be limited to the Code of Federal Regulations (United States); Ministry of Health, Labor, and Welfare (MHLW): Ethical Guidelines for Clinical Research (Japan); MHLW: Good Clinical Practice Guidelines (Japan); Japan Pharmaceuticals Affairs Law; the International Conference on Harmonisation Guideline for Good Clinical Practice; and the World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Patients.</td>
</tr>
<tr>
<td>Regulatory Agency</td>
<td>Throughout this document, the term <em>regulatory agency</em> refers to all applicable health and regulatory agencies. These may be international, national, or local, and may include but not be limited to MHLW (Japan), Pharmaceuticals and Medical Devices Agency (PMDA), European Medicines Agency (EMA), and the United States Food and Drug Administration (FDA).</td>
</tr>
<tr>
<td>Screening Period</td>
<td>The <em>screening period</em> for a patient begins when the informed consent form is signed and continues until the first dose of study drug is administered.</td>
</tr>
<tr>
<td>Sponsor</td>
<td>Throughout this document, the term <em>sponsor</em> refers to all applicable departments within Takeda Pharmaceutical Company Limited, or its designee.</td>
</tr>
<tr>
<td>Study Drug</td>
<td>For the purposes of this protocol, <em>study drug</em> refers to TAK-788.</td>
</tr>
<tr>
<td>Study Reference Manual</td>
<td>In the context of this study, <em>study reference manual</em> is a general term for the information provided to sites on technical aspects of the trial.</td>
</tr>
<tr>
<td>Study Start Date</td>
<td>The <em>study start date</em> is the date that the first patient signs the informed consent form.</td>
</tr>
<tr>
<td>Treatment Period</td>
<td>The <em>treatment period</em> is from time of first dose until 30 days past last dose.</td>
</tr>
</tbody>
</table>
8 INTRODUCTION

8.1 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 (i.e., 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 (WT) 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 WT EGFR.

The most common activating mutations in EGFR are in-frame deletions in exon 19 and a Leu858Arg (L858R) substitution in exon 21, together accounting for about 90% of all EGFR activating mutations [3]. Erlotinib and gefitinib (“first generation” EGFR TKIs), as well as afatinib (a “second generation” EGFR TKI), potently inhibit these mutants in vitro and induce high response rates of about 60%-70% in patients with these mutations [4]. Osimertinib has recently been approved in patients with common mutations as the first-line treatment option, following the first approval in patients with metastatic EGFR T790M mutation–positive NSCLC and who have progressed on or after EGFR TKI therapy [5,6]. Although these TKIs are approved for use in patients with these specific mutations, their clinical efficacy is ultimately limited by the development of resistance, such as by mutation of the EGFR kinase domain gatekeeper residue (T790M), which occurs in 50% of patients [7,8].

For erlotinib and gefitinib, high response rates have largely been restricted to patients with the most common activating mutants; however, preliminary results with afatinib suggest that relatively high response rates are also achieved in patients with a second class of activating mutants, so-called “uncommon” mutants, such as those occurring at other amino acids in exons 19 and 21 (e.g., G719X and L861) [9]. Afatinib was recently approved by the Food and Drug Administration (FDA) for a broadened indication in first-line treatment of patients with metastatic NSCLC whose tumors have nonresistant EGFR mutations to include patients whose tumors harbor uncommon mutations, such as L861Q, G719X, and S768I [10].

The final class of EGFR activating mutations, known as exon 20 insertions, account for approximately 9% of all EGFR mutant NSCLC [11]. Unlike mutations in exons 19 or 21, almost all EGFR exon 20 insertions confer in vitro and primary clinical resistance to the three approved EGFR TKIs [9,12,13]. Patients with NSCLC containing EGFR exon 20 insertions exhibit clinical characteristics similar to those carrying common EGFR mutations [14] (e.g., young, nonsmoker, with adenocarcinoma subtype), consistent with potential roles as driver mutations that could confer benefit to targeted therapy. In summary, while erlotinib, gefitinib, afatinib, and osimertinib are approved for use in NSCLC patients with common activating mutations in EGFR (i.e., exon 19 deletions and L858R substitutions) and afatinib was recently approved by the FDA for a broadened indication that includes the uncommon EGFR mutations, such as L861Q, G719X, and S768I, no targeted therapies are approved for patients with EGFR exon 20 insertions.
Human epidermal growth factor 2 (HER2) mutations, typically consisting of in-frame insertions in exon 20, have also been identified as potential oncogenic drivers in 2%-4% of NSCLC patients. These patients exhibit clinical characteristics similar to EGFR-mutated patients [15-17]. Currently, no therapies are approved for use in NSCLC patients with HER2 activating mutations.

8.1.1 Study Drug and Rationale

To address limitations of existing therapies targeting EGFR and HER2, the sponsor is developing TAK-788 (also known as mobocertinib and formerly AP32788), a novel, synthetic, orally-administered TKI. In nonclinical studies, TAK-788 potently inhibits all activated forms of EGFR tested, including those containing exon 20 activating insertions, other uncommon activating mutations, and the common activating mutations (exon 19 deletions and L858R) with or without the T790M resistance mutation. TAK-788 also potently inhibits HER2 activated by exon 20 insertions and point mutations, as well as by amplification. TAK-788 inhibits all of these variants more potently than it inhibits WT EGFR, suggesting it may have the selectivity necessary to achieve levels of exposure required to inhibit all activated forms of these kinases.

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

Based on the promising activity profile of TAK-788 in vitro and in vivo, as well as its toxicologic profile, a phase 1/2 first-in-human clinical trial of the agent will be conducted. The trial will be conducted in three parts: a dose escalation phase, followed by an expansion phase and a pivotal extension phase.

Part 1: Dose Escalation Cohorts

The patient population of the initial dose escalation phase of the trial will include patients with advanced NSCLC. The objectives of the dose escalation phase are to determine the safety, pharmacokinetic (PK) profile, and recommended phase 2 dose (RP2D) of orally administered TAK-788 in these patients.

Part 2: Expansion Cohorts

The dose and schedule for the expansion cohorts will be determined based on the RP2D and schedule determined in the dose escalation phase of the trial.

The expansion phase will include seven histologically and molecularly defined cohorts. The seven expansion cohorts will be:

1. NSCLC patients with EGFR exon 20 activating insertions, who have either not received or not shown an objective response to an EGFR TKI, and who have no active, measurable central nervous system (CNS) metastases;
2. NSCLC patients with HER2 exon 20 activating insertions or point mutations and no active, measurable CNS metastases;
3. NSCLC patients with EGFR exon 20 activating insertions or HER2 exon 20 activating insertions or point mutations and active, measurable CNS metastases;
4. NSCLC patients with other targets against which TAK-788 is active (examples include EGFR exon 19 deletions or exon 21 substitutions [with or without T790M mutations] and other uncommon EGFR activating mutations), without active CNS metastases;
5. NSCLC patients with EGFR exon 20 activating insertions, who have previously shown an objective response to or stable disease (SD) with an EGFR TKI and subsequently progressed, without active CNS metastases;

6. NSCLC patients with EGFR exon 20 activating insertions, who have not received prior systemic anticancer treatment for locally advanced or metastatic disease, without active CNS metastases; and

7. Patients with solid tumors other than NSCLC with EGFR/HER2 mutations against which TAK-788 is active (for details, see the cohort-specific inclusion criteria in Section 11.1.2), without active CNS metastases.

The safety and tolerability of orally administered TAK-788 will continue to be assessed in the expansion cohorts. However, the primary objective of the expansion component of the trial is to evaluate the anti-tumor activity of TAK-788 in these patient populations. Confirmed objective response rate (ORR), as assessed by the investigator per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), will be the primary endpoint in the expansion cohorts with the exception of Expansion Cohorts 3 and 6 (see Section 16.3.1).

Part 3: Extension Cohort

The extension cohort is an international, multicenter, open-label cohort and is designed to evaluate the efficacy of TAK-788 at 160 mg once daily (QD) in patients with locally advanced or metastatic NSCLC whose tumors harbor EGFR exon 20 insertion mutations and who have been previously treated. All patients in the extension cohort 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. The patients will be treated with 160 mg QD TAK-788, which is the RP2D selected based on data from the dose escalation phase and expansion cohorts. The confirmed ORR, as assessed by Independent Review Committee (IRC) per RECIST v1.1, will be the primary endpoint in the extension cohort. No targeted therapies are currently approved for patients with EGFR exon 20 insertions. The cohort is intended to be used for registrational purposes.

8.1.2 Rationale for RP2D

As of 21 March 2018, 57 patients had been treated with TAK-788 in the dose escalation phase of this study. Starting from the 40 mg QD cohort, initial signs of disease stabilization were reported in patients with EGFR exon 20 insertion mutations. The disease control rate (DCR)—the percentage of patients with best response of complete response [CR], partial response [PR], or SD) among 10 patients with EGFR exon 20 insertion mutations who had at least 1 disease assessment following treatment with TAK-788 in the 5 to 40 mg QD cohorts—was 30%. In the 80 mg QD or 40 mg twice-daily cohorts, among 9 patients with EGFR exon 20 insertion mutations who had at least 1 disease assessment following treatment with TAK-788, 2 patients were reported to have confirmed PRs, and 2 patients had PRs (waiting for confirmation as of the data lock); the DCR was 89%. In the 120 mg QD or 60 mg twice-daily cohorts, among 4 patients with EGFR exon 20 insertion mutations who had at least 1 disease assessment following treatment with TAK-788, 1 patient was reported to have a confirmed CR, and the DCR was 100%. In the 160 mg QD cohort, among 5 patients with EGFR exon 20 insertion mutations who had at least 1 disease assessment following treatment with TAK-788, 1 patient had a confirmed PR and 1 patient had a PR (waiting for confirmation as of the data lock); the DCR was 100%.
These observed responses suggest that TAK-788 may be able to reach the target exposures to selectively inhibit EGFR exon 20 mutations in humans. The steady state combined (TAK-788 and its 2 active metabolites) exposure (molar average concentration) for the responders was in the range of 53 nM to 203 nM (dose range of 80 mg QD to 160 mg QD) observed in the first-in-human clinical study, close to or exceeding the nonclinically determined 50% inhibitory concentration (IC50 = 58 nM after being corrected for the functional effect of protein binding on potency) to inhibit the exon 20 insertions.

In mid-January 2018, 160 mg QD was identified as the maximum tolerated dose (MTD). In combination with the efficacy, safety, and PK results observed in the dose escalation phase of this study, 160 mg QD was also recommended as the RP2D for Part 2 (phase 2 expansion cohorts).

Analysis supporting the early proof-of-concept assessment on the basis of Parts 1 and 2 of the study (the dose escalation and expansion phases) was conducted in August 2018 and confirmed that 160 mg QD was the RP2D for the Part 3 extension cohort. The unconfirmed ORR and DCR at the 160 mg QD dose were 47.6% (10 of 21) and 85.7% (18 of 21), respectively. With respect to the safety profile, the most common all-grade treatment-emergent adverse events (AEs) (greater than 20% incidence in all patients treated at doses ranging from 80 to 160 mg total daily dose) had the following incidences at 160 mg QD: diarrhea (71.9%), nausea (40.6%), vomiting (31.3%), and decreased appetite (28.1%). The most common Grade $\geq$3 treatment-emergent AE was diarrhea; the incidence was 15.6% at 160 mg QD. The dose reduction rate for patients who received 160 mg QD was 27.5%.

Analysis of the 120 mg dose also revealed a positive early proof-of-concept. The unconfirmed ORR and DCR were 33.3% (3 of 9) and 77.8% (7 of 9), respectively, at 120 mg QD. The approximately 14% lower observed ORR with 120 mg QD compared with 160 mg QD was considered clinically meaningful although not statistically significant given the limited sample size. The most common all-grade treatment-emergent AEs (greater than 20% incidence in all patients treated at doses ranging from 80 to 160 mg total daily dose) had the following incidences at 120 mg QD: diarrhea (85.7%), nausea (35.7%), decreased appetite (35.7%), and vomiting (7.1%). The incidence of Grade $\geq$3 diarrhea was 7.1% at 120 mg QD. Although Grade $\geq$3 diarrhea was more common at 160 mg QD than 120 mg QD, the incidence was still aligned with that observed with other EGFR TKIs. The dose reduction rate was also largely comparable: 25% at 120 mg total daily dose and 27.5% at 160 mg QD. Overall, the safety profile of TAK-788 was largely comparable between the 120 mg QD and 160 mg QD dosages, with slightly more gastrointestinal-related AEs (including nausea and vomiting) at the 160 mg QD dosage. The gastrointestinal-related AEs are considered manageable.

The emerging PK results showed a dose-proportional increase in drug exposure of TAK-788 combined with 2 active metabolites following a single dose of TAK-788. However, exposures following multiple-dose administration increased less than dose-proportionally, with the exposure at 160 mg QD following multiple-dose treatment (Cycle 2 PK) being comparable to 120 mg QD, which suggested autoinduction of the apparent oral clearance of TAK-788 at 160 mg QD. This autoinduction is likely explained by concentration-dependent induction of cytochrome P450 (CYP)3A by TAK-788. Preliminary exposure-efficacy analysis showed a relationship between the overall response rate and the combined exposure of TAK-788 and its 2 active metabolites.
Although autoinduction was observed at 160 mg QD resulting in lack of meaningful increase in steady state systemic exposures from 120 mg QD to 160 mg QD and indicating potential for TAK-788 to produce drug-drug interactions (DDI), 160 mg QD is considered as the RP2D based on the following rationale: 1) higher observed ORR; 2) comparable safety profile; and 3) given the high heterogeneity of EGFR exon 20 insertion mutations and their varied sensitivity to TAK-788, 160 mg QD is predicted to achieve sufficient exposure to inhibit most EGFR exon 20 insertion mutations, if not all.

8.1.3 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 (see Section 8.1.2). 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.
9 STUDY OBJECTIVES

Parts 1 and 2: Dose Escalation and Expansion Cohorts

The objectives of this study for the dose escalation and expansion cohorts are:

1. To determine the safety profile of orally administered TAK-788
2. To identify the RP2D, dose-limiting toxicities (DLTs), and the MTD of TAK-788
3. To determine the PK profile of TAK-788 and its active metabolites, AP32960 and AP32914
4. To evaluate the anti-tumor activity of TAK-788 in NSCLC with EGFR or HER2 mutations
5. To evaluate the anti-tumor activity of TAK-788 in patients with solid tumors other than NSCLC with EGFR or HER2 mutations

Part 3: Extension Cohort

The objectives of the study for the extension cohort are:

Primary: To determine the efficacy of TAK-788, as evidenced by confirmed ORR, as assessed by the IRC, in patients with locally advanced or metastatic NSCLC harboring EGFR in-frame exon 20 insertion mutations and who have received at least 1 prior line of therapy for locally advanced or metastatic NSCLC

Secondary:

1. To further characterize the efficacy of TAK-788 as shown by confirmed ORR, as assessed by the investigator, duration of response, progression free survival (PFS), DCR, time to response, and overall survival (OS)
2. To assess the safety and tolerability of TAK-788
3. To collect sparse plasma concentration-time data of TAK-788 and its active metabolites, 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

Exploratory:
10 INVESTIGATIONAL PLAN

10.1 Overall Study Design and Plan

This is an open-label, multi-center, dose escalation study (3+3 design initial dose escalation cohort) with expansion into seven histologically and molecularly defined expansion cohorts after the RP2D is established and a pivotal extension cohort following establishment of early proof-of-concept in patients with NSCLC with EGFR exon 20 insertion mutations. Patients enrolled in an expansion cohort or the extension cohort must meet the cohort-specific inclusion criteria for the given cohort, in addition to the general eligibility criteria. Figure 1 presents an illustration of the study design. Section 14.2.2 provides a detailed description of the 3+3 design implemented in this study.

Part 1: Dose Escalation Cohort

The patient population of the initial dose escalation phase of the trial will include patients with advanced NSCLC. The objectives of the dose escalation phase are to determine the safety, PK profile, and RP2D of orally administered TAK-788 in these patients. The RP2D is the MTD of TAK-788 or less. An RP2D less than MTD may be chosen if aspects of tolerability not encompassed by the MTD determination suggest utilizing a lower dose.

Part 2: Expansion Cohort

The expansion phase will include 7 additional histologically and molecularly defined cohorts, with Expansion Cohort 3 being limited to patients with active, measurable CNS metastases. The dose and schedule for the expansion cohorts will be determined based on the RP2D and schedule determined in the dose escalation phase of the trial. The decision to open the expansion cohort will be based on an assessment of safety and preliminary anti-tumor activity from the dose escalation cohort. The seven expansion cohorts will be:

1. NSCLC patients with EGFR exon 20 activating insertions, who have either not received or not shown an objective response to an EGFR TKI, and who have no active, measurable CNS metastases;
2. NSCLC patients with HER2 exon 20 activating insertions or point mutations and no active, measurable CNS metastases;
3. NSCLC patients with EGFR exon 20 activating insertions or HER2 exon 20 activating insertions or point mutations and active, measurable CNS metastases;
4. NSCLC patients with other targets against which TAK-788 is active (examples include EGFR exon 19 deletions or exon 21 substitutions [with or without T790M mutations] and other uncommon EGFR activating mutations), without active CNS metastases;
5. NSCLC patients with EGFR exon 20 activating insertions, who have previously shown an objective response to or SD with an EGFR TKI and subsequently progressed, without active CNS metastases;  
6. NSCLC patients with EGFR exon 20 activating insertions, who have not received prior systemic anticancer treatment for locally advanced or metastatic disease, without active CNS metastases; and  
7. Patients with solid tumors other than NSCLC with EGFR/HER2 mutations against which TAK-788 is active (for details, see the cohort-specific inclusion criteria in Section 11.1.2), without active CNS metastases.

The safety and tolerability of orally administered TAK-788 will continue to be assessed in the expansion cohorts. However, the primary objective of the expansion component of the trial is to evaluate the anti-tumor activity of TAK-788 in these patient populations. Confirmed ORR, as assessed by the investigator per RECIST v1.1, will be the primary endpoint in Expansion Cohorts 1, 2, 4, 5, and 7; intracranial CNS response rate, as assessed by the IRC, will be the primary endpoint in Expansion Cohort 3; and confirmed ORR, as assessed by the IRC per RECIST v1.1, will be the primary endpoint in Expansion Cohort 6.

Part 3: Extension Cohort

The extension cohort will receive open-label TAK-788 at 160 mg QD and will enroll patients with locally advanced or metastatic NSCLC whose tumors harbor EGFR exon 20 insertions and who have been previously treated. An estimated 91 patients will be enrolled at approximately 100 sites to include approximately 73 patients with central confirmation of EGFR exon 20 insertion mutations. The primary objective of the extension cohort is to determine the efficacy of TAK-788 by confirmed ORR as assessed by the IRC per RECIST v1.1. Secondary objectives include additional efficacy assessments and assessments of safety, tolerability, PK, and patient-reported outcomes including HRQoL.
Figure 1  Schematic of TAK-788 Phase 1/2 Trial Design – Dose Escalation, Expansion, and Extension Phases

**Cohort 4** will enroll at least 20 patients with an uncommon activating mutation, either alone or in combination with other EGFR mutations except exon 20 insertion mutations.

**Cohort 7** will enroll at least 20 patients with a HER2 activating mutation, either alone or in combination with other EGFR mutations.

* Cohort 4 will enroll at least 20 patients with an uncommon activating mutation, either alone or in combination with other EGFR mutations except exon 20 insertion mutations.

** Cohort 7 will enroll at least 20 patients with a HER2 activating mutation, either alone or in combination with other EGFR mutations.
10.2 Randomization and Blinding

This is an open-label dose escalation study with expansion into seven histologically and molecularly defined expansion cohorts after the RP2D is established and a pivotal extension cohort following establishment of early proof-of-concept in patients with NSCLC with EGFR exon 20 insertion mutations. Patients will not be randomized to treatments, and neither patients nor investigators will be blinded.

11 SELECTION OF STUDY POPULATION

11.1 Inclusion Criteria

11.1.1 General Inclusion Criteria (All Cohorts: Dose Escalation, Expansion, and Extension)

All patients must meet all of the following general inclusion criteria for study entry.

1. Have histologically or cytologically confirmed locally advanced (and not a candidate for definitive therapy) or metastatic disease (Stage IIIb or IV). For all cohorts except Expansion Cohort 7, the locally advanced or metastatic disease is NSCLC. For Expansion Cohort 7, the locally advanced or metastatic disease is any solid tumor other than NSCLC.

2. Must have sufficient tumor tissue available for analysis (see Laboratory Manual for specific requirements). For patients in the expansion cohorts and in the extension cohort, tumor tissue obtained after progression on the most recent prior therapy is preferred.

3. Must have measurable disease by RECIST v1.1 (Appendix B).

4. Male or female adult patients (aged 18 years or older, or as defined per local regulations).

5. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1 (Appendix A).

6. Minimum life expectancy of 3 months or more.

7. Adequate renal and hepatic function as defined by the following criteria:
   a. Total serum bilirubin $\leq 1.5 \times$ upper limit of normal (ULN) ($\leq 3.0 \times$ ULN for patients with Gilbert syndrome or if liver function abnormalities are due to underlying malignancy);
   b. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq 2.5 \times$ ULN (or $\leq 5 \times$ ULN if liver function abnormalities are due to underlying malignancy);
   c. Estimated creatinine clearance $\geq 30$ mL/min (calculated by using the Cockcroft-Gault equation);
   d. Serum albumin $\geq 2$ g/dL;
   e. Serum lipase $\leq 1.5 \times$ ULN; and
   f. Serum amylase $\leq 1.5 \times$ ULN unless the increased serum amylase is due to salivary isoenzymes.
8. Adequate bone marrow function as defined by the following criteria:
   a. Absolute neutrophil count (ANC) ≥1.5 × 10⁹/L;
   b. Platelet count ≥75 × 10⁹/L; and
   c. Hemoglobin ≥9.0 g/dL.

9. Normal QT interval on screening electrocardiogram (ECG), defined as QTcF of ≤450 ms in males or ≤470 ms in females.

10. 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 [18]), 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.

11. Female patients who:

   • Are postmenopausal for at least 1 year before the screening visit, OR
   • Are surgically sterile, OR
   • If they are of childbearing potential, agree to practice 1 highly effective, nonhormonal method of contraception and 1 additional effective (barrier) method (Table 5) at the same time, from the time of signing the informed consent through 30 days after the last dose of study drug, OR
   • Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

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

   • Agree to practice effective barrier contraception during the entire study treatment period and through 30 days after the last dose of study drug, OR
   • Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

12. Signed and dated informed consent indicating that the patient has been informed of all pertinent aspects of the study.

13. Willingness and ability to comply with scheduled visits and study procedures.

11.1.2 Cohort-Specific Inclusion Criteria

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

Part 1: Dose escalation cohorts

1. Refractory to standard available therapies.
Part 2: Expansion cohorts

Expansion Cohort 1: NSCLC patients with EGFR exon 20 activating insertions, who have either not received or not shown an objective response to an EGFR TKI, and who have no active, measurable CNS metastases

1. Have a documented EGFR in-frame exon 20 insertion by a local test, including A763_Y764insFQEA, V769_D770insASV, D770_N771insNPG, D770_N771insSVD, H773_V774insNPH, or any other in-frame exon 20 insertion mutation. The EGFR exon 20 insertion mutation can be either alone or in combination with other EGFR or HER2 mutations.
2. Previously treated with one or more regimens of systemic therapy for locally advanced or metastatic disease.
3. Prior treatment with an EGFR TKI is allowed unless the patient had an objective response and subsequent progression as assessed by the investigator or treating physician during treatment with that prior TKI.

Expansion Cohort 2: NSCLC patients with HER2 exon 20 activating insertions or point mutations and no active, measurable CNS metastases

1. Have one of the following documented by a local test:
   a. A HER2 exon 20 insertion including A775_G776insYVMA, G776_V777insVC, or P780_Y781insGSP, or any other in-frame exon 20 insertion mutation.
   b. An activating point mutation in HER2 including, but not limited to, L755S, G776V, and V777L.

   The HER2 exon 20 insertion mutation or point mutation can be either alone or in combination with other EGFR mutations except EGFR exon 20 insertion mutations.
2. Previously treated with one or more regimens of systemic therapy for locally advanced or metastatic disease.
3. Prior treatment with a pan-HER TKI (eg, afatinib, neratinib, or dacomitinib) is allowed unless the patient had an objective response and subsequent progression as assessed by the investigator or treating physician during treatment with that prior TKI.

Expansion Cohort 3: NSCLC patients with EGFR exon 20 activating insertions or HER2 exon 20 activating insertions or point mutations and active, measurable CNS metastases

1. Have one of the following documented by a local test:
   b. A HER2 exon 20 insertion: A775_G776insYVMA, G776_V777insVC, P780_Y781insGSP, or any other in-frame exon 20 insertion mutation.
   c. An activating point mutation in HER2 including, but not limited to, L755S, G776V, and V777L.

   The above mutations can be either alone or in combination with other EGFR mutations.
2. Previously treated with one or more regimen of systemic therapy for locally advanced or metastatic disease.

3. For patients with an EGFR exon 20 insertion: prior treatment with an EGFR TKI is allowed unless the patient had an objective response and subsequent progression as assessed by the investigator or treating physician during treatment with that prior TKI.

4. For patients with a HER2 exon 20 insertion or HER2 activating point mutation: prior treatment with a pan-HER TKI (eg, afatinib, neratinib, or dacomitinib) is allowed unless the patient had an objective response and subsequent progression as assessed by the investigator or treating physician during treatment with that prior TKI.

5. Have either previously untreated intracranial CNS metastases or previously treated intracranial CNS metastases with radiologically documented new or progressing CNS lesions.

6. Have at least one target (ie, measurable) intracranial CNS lesion (≥10 mm in longest diameter by contrast enhanced magnetic resonance imaging [MRI]). Lesions previously treated by stereotactic radiosurgery (SRS) or surgical resection should not be included as a target lesion. Lesions previously treated with whole brain radiation therapy (WBRT) may be included as a target lesion if (1) the last administration of WBRT was >3 months prior to the first dose of TAK-788 and (2) unequivocal radiological progression of the lesion has been observed.

Expansion Cohort 4: NSCLC patients with other targets against which TAK-788 is active, without active CNS metastases

1. Have one of the following documented by a local test: an activating mutation in EGFR including exon 19 deletions or exon 21 L858R substitution (with or without T790M), or an uncommon activating mutation other than exon 20 insertion including, but not limited to, G719X (where X is any other amino acid), S768I, L861Q, or L861R.

2. Treatment naïve for locally advanced or metastatic disease or previously treated with one or more regimens of systemic therapy for locally advanced or metastatic disease.

Expansion Cohort 5: NSCLC patients with EGFR exon 20 activating insertions, who have previously shown an objective response to or SD with an EGFR TKI and subsequently progressed, without active CNS metastases

1. Have a documented EGFR in-frame exon 20 insertion by a local test, including A763_Y764insFQEA, V769_D770insASV, D770_N771insNPG, D770_N771insSVD, H773_V774insNPH, or any other in-frame exon 20 insertion mutation. The EGFR exon 20 insertion mutation can be either alone or in combination mutation with other EGFR or HER2 mutations.

2. Previously treated with one or more regimens of systemic therapy for locally advanced or metastatic disease.

3. Previously showed an objective response to an EGFR TKI or SD for at least 6 months with an EGFR TKI, then subsequently progressed as assessed by the investigator or treating physician.
Expansion Cohort 6: NSCLC patients with EGFR exon 20 activating insertions, who have not received prior systemic anticancer treatment for locally advanced or metastatic disease, without active CNS metastases

1. Have a documented EGFR in-frame exon 20 insertion by a local test, including A763_Y764insFQEA, V769_D770insASV, D770_N771insNPG, D770_N771insSVD, H773_V774insNPH, or any other in-frame exon 20 insertion mutation. The EGFR exon 20 insertion mutation can be either alone or in combination with other EGFR or HER2 mutations.
2. No prior systemic treatment for locally advanced or metastatic disease (with the exception below):
   Prior adjuvant chemotherapy for Stage I to III or combined modality chemotherapy/radiation for locally advanced disease is allowed if completed >12 months prior to the first dose of TAK-788.

Expansion Cohort 7: Patients with solid tumors other than NSCLC with EGFR/HER2 mutations against which TAK-788 is active, without active CNS metastases

1. Have a locally advanced or metastatic solid tumor that is not NSCLC, including, but not limited to, bladder/urinary tract cancer, breast cancer, gastric/esophageal cancer, biliary tract cancer, and head and neck cancer.
2. Is refractory to standard therapy.
3. Have a target against which TAK-788 is active, documented by a local test, including, but not limited to, the following:
   a. An activating mutation in EGFR including exon 20 insertions, exon 19 deletions or exon 21 L858R substitution (with or without T790M), or an uncommon activating mutation including G719X (where X is any other amino acid), S768I, L861Q, or L861R.
   b. A HER2 exon 20 insertion: A775_G776insYVMA, G776_V777insVC, P780_Y781insGSP, or any other in-frame exon 20 insertion mutation.
   c. An activating point mutation in HER2 including, but not limited to, L755S, G776V, and V777L.

Part 3: Extension cohort

1. Have 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) assessed by a Clinical Laboratory Improvements Amendment (CLIA)-certified (United States [US] sites) or an accredited (outside of the US) local laboratory and sufficient tumor tissue available for central analysis (see Laboratory Manual). The EGFR exon 20 insertion mutation can be either alone or in combination with other EGFR or HER2 mutations. Note: central confirmation is not required for enrollment.
2. Must have received at least 1 prior line of therapy for locally advanced or metastatic disease and no more than 2 regimens of systemic anticancer chemotherapies for locally advanced or metastatic disease.
Note: A systemic anticancer chemotherapy regimen will be counted if it is administered over at least 1 cycle. A new antineoplastic chemotherapy used as maintenance therapy will be counted as a new regimen. Neoadjuvant or adjuvant systemic anticancer chemotherapy will be counted as a prior regimen if completion of the (neo)adjuvant therapy occurred <12 months prior to enrollment.

Prior treatment with an EGFR TKI is allowed unless the patient had an objective response and subsequent progression as assessed by the investigator or treating physician during treatment with that prior TKI.

### 11.2 Exclusion Criteria

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

1. Previously received TAK-788.
2. Received small-molecule anticancer therapy (including cytotoxic chemotherapy and investigational agents) ≤14 days prior to first dose of TAK-788 (except for reversible EGFR TKIs [ie, erlotinib or gefitinib], which are allowed up to 7 days prior to the first dose of TAK-788).
3. Received antineoplastic monoclonal antibodies including immunotherapy within 28 days of the first dose of TAK-788.
4. 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. Note: This exclusion criterion does not apply to Expansion Cohort 7.
5. Received radiotherapy ≤14 days prior to the first dose of TAK-788 or has not recovered from radiotherapy-related toxicities. Palliative radiation administered outside the chest and brain, SRS, and stereotactic body radiotherapy are allowed up to 7 days prior to the first dose.
6. 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 C).
7. 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.
8. Part 1 (dose escalation) and Expansion Cohorts 1 to 3 of Part 2 (expansion phase) only: Have symptomatic CNS metastases at screening or asymptomatic disease requiring corticosteroids to control symptoms within 7 days prior to the first dose of TAK-788.

Part 3 (extension cohort) and Expansion Cohorts 4 to 7 of Part 2 (expansion phase) only: Have known active brain metastases (have either previously untreated intracranial CNS metastases or previously treated intracranial CNS metastases with radiologically documented new or progressing CNS lesions). Brain metastases are allowed if they have
been treated with surgery and/or radiation and have been stable without requiring corticosteroids to control symptoms within 7 days before the first dose of TAK-788, and have no evidence of new or enlarging brain metastases.

9. Have current spinal cord compression (symptomatic or asymptomatic and detected by radiographic imaging) or leptomeningeal disease (symptomatic or asymptomatic).

10. Have significant, uncontrolled, or active cardiovascular disease, including, but not restricted to:
   a. Myocardial infarction (MI) within 6 months prior to the first dose of study drug;
   b. Unstable angina within 6 months prior to first dose;
   c. Congestive heart failure (CHF) within 6 months prior to first dose;
   d. History of clinically significant (as determined by the treating physician) atrial arrhythmia;
   e. Any history of ventricular arrhythmia; or
   f. Cerebrovascular accident or transient ischemic attack within 6 months prior to first dose.

11. Have a known history of uncontrolled hypertension. Patients with hypertension should be under treatment on study entry to control blood pressure.

12. Have prolonged QTcF interval, or being treated with medications known to be associated with the development of Torsades de Pointes (Appendix D).

13. (Parts 1 and 2 [dose escalation and expansion cohorts] only) Have an ongoing or active infection including, but not limited to, the requirement for intravenous (IV) antibiotics, or a known history of human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV). Testing is not required in the absence of history.

   (Part 3 [extension cohort] only) Have an ongoing or active infection including, but not limited to, the requirement for IV antibiotics, or a known history of HIV. Testing is not required in the absence of history.

   (Part 3 [extension cohort] only) Hepatitis B surface antigen (HBsAg) positive patients are allowed to enroll if HBV DNA is below 1000 copies/mL in the plasma. Patients who are positive for anti-HCV antibody (HCVAb) can be enrolled but must not have detectable HCV RNA in the plasma.

14. Currently have or have a history of interstitial lung disease, radiation pneumonitis that required steroid treatment, or drug-related pneumonitis.

15. Female patients who are lactating and breastfeeding or have a positive urine or serum pregnancy test during the screening period. Note: Female patients who are lactating will be eligible if they discontinue breastfeeding.

16. Have gastrointestinal illness or disorder that could affect oral absorption of TAK-788.

17. 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.
12 STUDY PROCEDURES

The screening period begins when the informed consent form is signed, and continues until the first dose of study drug is administered. The follow-up period begins at the end of treatment and continues until patient contact discontinues.

12.1 Study Procedure Descriptions

The study procedures to be performed at screening and throughout the entire study are listed for Parts 1 and 2 (the dose escalation and expansion cohorts) in Table 1 (Schedule of Events) and for Part 3 (the extension cohort) in Table 2 (Schedule of Events), which are meant to provide a convenient display of the timing and scope of required assessments expected at each visit, but do not provide a comprehensive description of each assessment. A complete list of all study-related assessments as well as a detailed description of what is expected in the assessment is included below. 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 visit unless otherwise noted in the Schedule of Events descriptions or table. A cycle is defined as 28 days.

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

The main treatment period is defined as the first 3 years of treatment. Patients who continue to receive TAK-788 after 3 years of treatment enter the treatment continuation period. Patients who continue to receive study drug 3 years after the last patient enrolls may be eligible to continue to receive posttrial access to TAK-788 (Section 12.8.4).

The following list describes the footnotes for Table 1 and Table 2.

1. Screening

Screening assessments must be performed no more than 14 days prior to Cycle 1, Day 1. The allowable window for the tumor imaging screening assessment is 21 days prior to Cycle 1, Day 1. However, whenever feasible, baseline imaging should be performed as close as possible to Cycle 1, Day 1.

Vital signs should be repeated on Cycle 1, Day 1 prior to first dose, regardless of the time from screening. Patient-reported outcome assessments (Part 3 extension cohort only), physical examination, ECOG Performance Status assessments, hematology, chemistry, urinalysis, serology (Part 3 extension cohort only), and pregnancy test assessments do not need to be repeated on Cycle 1, Day 1 if they were performed for screening within 7 days prior to Cycle 1, Day 1 and, in the opinion of the investigator, there is no reason to believe they have substantially changed.
2. Informed Consent

Patients will be given an informed consent for review and signature; patients consenting via the eConsent, where this is available, will electronically sign consent forms (paper consents will be used if required by local regulations). eConsent provides the same information as in written consent, but in an electronic format that may include multimedia components. It is important to note that eConsent is not meant to replace the important discussion between the participant and site staff. As with traditional consenting, the site will continue to own the consenting process. The requirements of informed consent are described in Section 18.2.

Informed consent, documented by a signed and dated consent form, must be obtained prior to any screening activities that are not otherwise considered part of normal patient care. Informed consent can be signed prior to the 14-day screening period window.

3. Demographics

Demographic information will be obtained at screening, and consists of the patient’s age, sex, race, and ethnicity (as allowed by local law and regulations).

4. Medical/Surgical History

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

5. 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.

6. Mutation Status

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

Part 3: Extension Cohort

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 a CLIA-certified (US sites) or an accredited (outside of the US) local laboratory. Local mutation testing can be conducted from either tumor specimen or liquid biopsy.

7. 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 (e.g., biopsy). Radiation will include both definitive and palliative treatment. Systemic therapy includes all regimens given, type of regimen (e.g., 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.

8. 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 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. Vital Signs

Vital signs include temperature, pulse, respiratory rate, and blood pressure (when patient is seated). In addition, the screening assessment must include height and weight. Vital signs should be repeated on Cycle 1, Day 1 prior to first dose, regardless of the time from screening. Vital signs will also be assessed per the Schedule of Events throughout the study.

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 throughout the study. The ECOG performance scale is provided in Appendix A.

11. Patient-Reported Outcome Assessments (for Part 3 [Extension Cohort] Only)

The EORTC QLQ-C30, EORTC QLQ-LC13, and HCC questionnaires will be administered at baseline, per the Schedule of Events throughout the study, and at the 30 Days After Last Dose visit for the extension cohort. The questionnaires should be administered to patients when they arrive for their scheduled visits, prior to any clinical measurements, assessments, evaluations, or procedures being performed.

12. Hematology, Clinical Chemistry, Urinalysis, and Serology

Hematology, clinical chemistry, and urinalysis assessments will be performed according to the Schedule of Events throughout the study. Hematology assessments will include complete blood count (CBC) with 5-part differential, hemoglobin, and platelet count. Chemistry assessments will include the following: sodium, potassium, chloride, bicarbonate (or total carbon dioxide), blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, aspartate transaminase (AST/serum glutamic oxaloacetic transaminase [SGOT]), alanine transaminase (ALT/serum glutamic pyruvic transaminase [SGPT]), bilirubin (at least total and direct, or total and indirect), alkaline phosphatase, magnesium, phosphorous, calcium, amylase, and lipase. Urinalysis will include pH, specific gravity, protein, ketone, glucose, urobilinogen, and occult blood.

(Part 3 [extension cohort] only) HBV and HCV testing will be performed at screening. As appropriate and according to local guidelines for the management of HBV infection, HBV screening may include the following: HBsAg, hepatitis B surface antibody, and hepatitis B core antibody. Patients who are HBsAg positive will also be tested for HBV
DNA. HBsAg-positive patients are allowed to enroll if HBV DNA is below 1000 copies/mL in the plasma with HBV DNA monitoring every 12 weeks. Initiation of antiviral treatment should follow local practice if HBV DNA >1000 copies is detected in the plasma during the study. HCV screening will include HCVAb. Patients who test positive for HCVAb will also be tested for HCV RNA at screening.

13. 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 at study start must also complete the pregnancy test once every 4 weeks thereafter and at the End-of-Treatment assessment.

14. Electrocardiogram

All ECGs must be 12-lead ECGs. An ECG is required at screening to determine eligibility; this may be a single ECG. 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). For consistency, the Fridericia correction – QTcF – method must be used for all calculations of QTc intervals.

Parts 1 and 2: Dose Escalation and Expansion Cohorts

Triplicate ECGs must be taken on Cycle 1, Day 1 before the first dose of TAK-788. Triplicate ECGs must be taken on Cycle 2, Day 1 (Day 29) prior to administration of the Cycle 2, Day 1 dose, and at 1, 2, 4, and 6 hours after dosing of TAK-788. Triplicate ECGs should be taken 1 to 2 minutes apart over a 5-minute timeframe. ECG measurements should coincide with the PK measurements that have the same time points. As such, triplicate ECGs should be taken directly before obtaining the PK sample at the allotted time points on Cycle 1, Day 1 and Cycle 2, Day 1. Adjustments to the timing of triplicate ECGs on Cycle 2, Day 1 may be made based on the PK findings in the dose escalation phase. Subsequent ECGs (after Cycle 2, Day 1) will be single ECGs.

ECGs will be recorded electronically and will be evaluated centrally.

Part 3: Extension Cohort

All ECGs will be a single ECG for the extension cohort. ECG measurement should be performed prior to the administration of TAK-788. Repeat testing during screening and throughout the study is permitted. ECGs will be evaluated centrally for sites in the US and locally for sites outside of the US.

15. Adverse Events

AEs are to be recorded continuously from the time of informed consent throughout the entire study until at least 30 days after the last dose of study drug and graded per NCI CTCAE v4.0 (before Amendment 3) and NCI CTCAE v5.0 (after Amendment 3). It is
expected that new and updated AEs and concomitant medications reported within the treatment period, ongoing AEs thought to be at least possibly study drug related, and all ongoing serious adverse events (SAEs) should be followed at least every 4 weeks until they resolve to baseline (or to NCI CTCAE v5.0 Grade ≤1), stabilize, or are considered to be chronic/irreversible.

16. Concomitant Medications

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 at least 30 days after the last dose, and for all concomitant treatments related to serious or study drug-related toxicities until the medication is no longer taken or until patient contact discontinues.

17. Blood Samples for Pharmacokinetic Analysis

Blood samples will be collected at pre-specified time points (pre- and post-dosing) to assess the plasma concentrations of TAK-788 and active metabolites (AP32960 and AP32914) and PK parameters following a single dose and multiple doses (steady state), in both the dose escalation and expansion cohorts. Sparse plasma concentration-time data of TAK-788 and its active metabolites, AP32960 and AP32914, in the extension cohort will be pooled with the data from the dose escalation and expansion cohorts to contribute to population PK and exposure-response analyses.

Parts 1 and 2: Dose Escalation and Expansion Cohorts

For patients in the dose escalation phase, 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 Cycle 1, Day 1. The 24-hour sample will be collected prior to drug administration on Cycle 1, Day 2. Blood samples will be collected prior to dosing on Cycle 1, Days 8, 15, and 22. 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 Cycle 2, Day 1. The 24-hour sample will be collected prior to drug administration on Cycle 2, Day 2. A PK sample will also be collected pre-dose on Cycle 3, Day 1.

For the expansion cohorts, PK sampling time points are initially planned to be the same as the sampling time points described above for the dose escalation phase; however, adjustments may be made based on the PK findings in the dose escalation phase.

Part 3: Extension Cohort

For patients in the extension cohort, blood samples will be collected at pre-specified time points (pre- and post-dosing) to assess the plasma concentrations of TAK-788 and its active metabolites (AP32960 and AP32914) for population PK and exposure-response analyses. The following plasma PK samples will be collected in all patients:

- Cycle 1, Day 1: 1 to 2 hours (±10 min) post-dose.
- Cycle 1, Day 15: pre-dose and 2 to 4 hours (±20 min) post-dose.
- Cycle 2, Day 1: pre-dose and 4 to 6 hours (±30 min) post-dose.
• Cycle 3, Day 1: pre-dose and 1 to 2 hours (±10 min) post-dose.
• Cycle 4, Day 1: pre-dose and 2 to 4 hours (±20 min) post-dose.
• Cycle 5, Day 1: pre-dose and 4 to 6 hours (±30 min) post-dose.

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 Cycle 1, Day 1) 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.

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 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. Previously irradiated lesions may not be used for target lesions, unless there is unambiguous radiological progression after radiotherapy.

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.

Target and non-target lesions must be selected at study start and assessed throughout the course of treatment according to RECIST v1.1 guidelines.

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.

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 End-of-Treatment. 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 at the same institution should be used at each assessment, if possible. All radiographic images (eg, CT scan, MRI) performed during the trial will be submitted to and stored by an imaging core lab for future independent evaluation as appropriate. A central IRC will evaluate all images collected during the study from patients enrolled in the Phase 2 expansion and extension cohorts.

19. Tumor Tissue Sample

At screening, all patients must submit an available formalin-fixed, paraffin-embedded (FFPE) tumor tissue for molecular profiling and exploratory biomarker studies, including
but not limited to molecular genetic analysis of EGFR, HER2, and other genes implicated in tumor biology. The tumor tissue may be archived or a fresh tissue sample if archived tumor tissue is not available during screening. For patients in the expansion cohorts and in the extension cohort, tumor tissue obtained after progression on the most recent prior therapy is preferred.

**Part 3: Extension Cohort**

All patients in the extension cohort must submit an available FFPE tumor tissue sample during screening for confirmation of mutation status by central testing.

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.
23. Treatment Continuation Period

Patients who continue to receive TAK-788 after 3 years of treatment enter the treatment continuation period. Details about the assessments during this period are provided in Table 1 and Table 2.

24. End-of-Treatment Assessments

End-of-Treatment assessments must be performed within 14 days of the patient’s last dose of study drug or the patient/investigator decision to discontinue study treatment, whichever occurs later. Physical examinations, laboratory tests (hematology, chemistry, 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.

25. 30 Days After Last Dose

The 30 Days After Last Dose assessments must be performed within 30 days (±7 days) after the last dose of study treatment. Physical examinations, laboratory tests (hematology, chemistry, 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 both the End-of-Treatment and 30 Days After Last Dose assessments, information may be collected from tests performed for the study or as part of the patient’s routine medical care.

26. Follow-up

Follow-up assessments (ie, contacting the patient for survival and subsequent anticancer therapy) must be performed every 12 weeks (±14 days) after the End-of-Treatment assessment. All new systemic anticancer therapies should be reported.

12.1.1 Schedule of Events

Table 1 and Table 2 list the screening and study procedures to be performed through the end of the study for the dose escalation/expansion cohorts and the extension cohort, respectively. Unless otherwise specified, the timing in which Cycle 1 tests are performed should be repeated in later cycles. Cycle visit samples or activities should occur within 3 days of the scheduled study day unless otherwise noted in the Schedule of Events.
<table>
<thead>
<tr>
<th>Assessment</th>
<th>Screening†</th>
<th>Main Treatment Period</th>
<th>Treatment Continuation Period‡</th>
<th>End of Treatment§</th>
<th>30 Days After Last Dose¶</th>
<th>Follow-up‖</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cycle 1</td>
<td>Cycle 2</td>
<td>Every 4 weeks</td>
<td>Every 8 weeks</td>
<td>Every 12 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D1</td>
<td>D2</td>
<td>D8</td>
<td>D15</td>
<td>D22</td>
</tr>
<tr>
<td>Informed consent†</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics†</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical/surgical history†</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis and cancer history†</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutation status‡</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior cancer therapy‡</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical examination§</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Vital signs§</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>ECOG Performance Status§</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hematology/chemistry/urinalysis†</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy test†</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Electrocardiogram (ECG)§</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triplet ECG§</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAK-788 administration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events§ †</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant medications§†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PK sampling†</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X (C3 only)</td>
</tr>
<tr>
<td>Disease assessment†</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Schedule of Events (Parts 1 and 2: Dose Escalation and Expansion Cohorts)
<table>
<thead>
<tr>
<th>Assessment</th>
<th>Screening&lt;sup&gt;§&lt;/sup&gt;</th>
<th>Main Treatment Period</th>
<th>Treatment Continuation Period&lt;sup&gt;§&lt;/sup&gt;</th>
<th>End of Treatment&lt;sup&gt;§&lt;/sup&gt;</th>
<th>30 Days After Last Dose&lt;sup&gt;§&lt;/sup&gt;</th>
<th>Follow-up&lt;sup&gt;§&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cycle 1</td>
<td>Cycle 2</td>
<td>Every 4 weeks</td>
<td>Every 8 weeks</td>
<td>Every 12 weeks</td>
</tr>
<tr>
<td>Day (D)</td>
<td>D1</td>
<td>D2</td>
<td>D8</td>
<td>D15</td>
<td>D22</td>
<td>D1</td>
</tr>
<tr>
<td>Tumor tissue at disease progression&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subsequent anticancer therapy/survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>C</sup>=Cycle, <sup>D</sup>=Day.
<sup>a</sup>After 3 years of treatment.
<sup>b</sup>Disease assessments begin the 12-week schedule on C14D28.
For footnotes, see Section 12.1.
Table 2  Schedule of Events (Part 3: Extension Cohort)

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Screening1</th>
<th>D1</th>
<th>D15</th>
<th>D1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day (D)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Informed consent2</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical/surgical history4</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis and cancer history5</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutation status6</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior cancer therapy1</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical examination2</td>
<td>X</td>
<td>X'</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Vital signs3</td>
<td>X</td>
<td>X'</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>ECOG Performance Status10</td>
<td>X</td>
<td>X'</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Patient-reported outcomes11</td>
<td>X</td>
<td>X'</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hematology/chemistry/urinalysis12</td>
<td>X</td>
<td>X'</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Serology13</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy test13</td>
<td>X</td>
<td>X'</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Electrocardiogram (ECG)14</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>TAK-788 administration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events15 “Concomitant medications”16</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PK sampling17</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Discharge assessment18</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Every 4 weeks</th>
<th>Every 8 weeks</th>
<th>Every 12 weeks</th>
<th>Every 12 weeks a</th>
<th>End of Treatment21</th>
<th>30 Days After Last Dose22</th>
<th>Follow-up23</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Applicable
2. Property
3. Takeda:

4. Non-Commercial

 pours pefc

Subject to the Applicable Terms of Use

Amendment: 02 September 2020
<table>
<thead>
<tr>
<th>Assessment</th>
<th>Screening(^1)</th>
<th>Main Treatment Period</th>
<th>Treatment Continuation Period(^3)</th>
<th>End of Treatment(^2)</th>
<th>30 Days After Last Dose(^5)</th>
<th>Follow-up(^6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cycle 1 Every 4 weeks Every 8 weeks Every 12 weeks Every 12 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day (D)</td>
<td></td>
<td></td>
<td>D1 D15 D1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCI</td>
<td></td>
<td></td>
<td>X (at disease progression)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tumor tissue at disease progression\(^5\)

Subsequent anticancer therapy/survival

CCI = Cycle, D = Day, HBsAg = hepatitis B surface antigen positive.

\(^5\) After 3 years of treatment.

\(^6\) Disease assessments begin the 12-week schedule on C14D28. Patient-reported outcomes begin the 12-week schedule on C15D1.

For footnotes, see Section 12.1.
12.2 Screening Period
The screening period begins when the informed consent form is signed, and continues until the patient receives the first dose of TAK-788. See Section 12.1 for further details.

12.3 Screen Failures
Patients who have signed informed consent and subsequently fail to meet the inclusion and/or exclusion criteria are defined as screen failures. Once the investigator determines that screening will not continue for a patient and the patient will not be enrolled in the study, the screen failure should be documented on the Eligibility Criteria eCRF within 5 days. For all screen failures, the investigator is to maintain a screening log that documents the patient initials and reason(s) for screen failure. A copy of the log should be retained in the investigator’s study files. All AEs and SAEs must be reported during the screening period until the patient has been determined to be a screen failure. Patients who screen fail may later be re-screened with prior sponsor approval.

12.4 Treatment Through 30 Days after Last Dose of Study Drug
The main treatment period begins when the patient receives the first dose of study drug. Patients who continue to receive TAK-788 after 3 years of treatment enter the treatment continuation period.

Assessments required during these periods are shown in Table 1 (Parts 1 and 2 [dose escalation and expansion cohorts]) and Table 2 (Part 3 [extension cohort]) with designated study assessments for the main treatment period (Cycle 1 until 3 years of treatment) and treatment continuation period (after 3 years of treatment). A detailed description of procedures and timing is provided in Section 12.1. Patients who continue to receive study drug 3 years after the last patient enrolls may be eligible to continue to receive posttrial access to TAK-788 (Section 12.8.4).

Note: Clinical laboratory assessments do not need to be repeated on Cycle 1, Day 1 if they were performed for screening within 7 days prior to Cycle 1, Day 1.

12.5 End of Treatment or Early Termination
End of Treatment is defined as the point when the patient or investigator decide to end study drug (which may be after a dose interruption). Assessments required at End of Treatment are shown in Table 1 (Parts 1 and 2 [dose escalation and expansion cohorts]) and Table 2 (Part 3 [extension cohort]). A detailed description of procedures and timing is provided in Section 12.1.

12.6 30 Days After Last Dose
Assessments required at 30 Days After Last Dose are shown in Table 1 (Parts 1 and 2 [dose escalation and expansion cohorts]) and Table 2 (Part 3 [extension cohort]). A detailed description of procedures and timing is provided in Section 12.1.

12.7 Follow-up Period Procedures
The follow-up period for a patient begins after End of Treatment (ie, when all study drug has been discontinued) and continues until patient contact ceases (for at least 3 years after the last patient has enrolled).
Assessments required for the Follow-up Period are shown in Table 1 (Parts 1 and 2 [dose escalation and expansion cohorts]) and Table 2 (Part 3 [extension cohort]). A detailed description of procedures and timing is provided in Section 12.1.

12.8 Study Duration

12.8.1 Study Completion Definition

The study will be completed 3 years after the last patient is enrolled, unless stopped earlier due to futility or sponsor decision.

12.8.2 Approximate Duration of Patient Participation

After a 2- to 3-week screening period, patients will 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. Patients will have an assessment at 30 days after treatment discontinuation. In addition, patients should be followed for survival at least every 3 months, until at least 3 years after the last patient has enrolled.

12.8.3 Approximate Duration of Study

The total estimated duration of the dose escalation and expansion components of the study is approximately 6 years, including 36 months to accrue patients with 3 years for treatment and follow-up after the last patient enrolls. The total estimated duration of the extension cohort component of the study is approximately 4 years, including approximately 13 months to accrue patients and 3 years for treatment and follow-up of the last patient. Patients who are still on study at 3 years will be allowed to receive study drug beyond 3 years until disease progression or until they discontinue treatment for other reasons. Refer to Section 12.8.4 for posttrial access to TAK-788 for patients still receiving study drug 3 years after the last patient has enrolled.

12.8.4 Posttrial Access

The clinical study database will be closed approximately 3 years after the last patient has enrolled. Patients in all cohorts will be allowed to continue treatment if, in the opinion of the investigator and confirmed by the sponsor, the patient has experienced a clinically important benefit from TAK-788, has no alternative therapeutic option, and would be harmed without continued access.

Duration of Posttrial Access

Continued access to TAK-788 for patients will be terminated for those individuals who no longer benefit from TAK-788, the benefit-risk no longer favors the individual, if TAK-788 becomes available either commercially or via another access mechanism, or when an alternative appropriate therapy becomes available. Posttrial access may be terminated in a country or geographical region where marketing authorization has been rejected, the development of TAK-788 has been suspended or stopped by the sponsor, or TAK-788 can no longer be supplied.
12.9 **Patient Discontinuation**

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

- Intolerable toxicity as determined by the investigator
- Progression of disease requiring an alternate therapy, in the opinion of 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 14.2.4.1). Patients who meet these discontinuation rules must not receive further dosing with TAK-788 unless the investigator discusses the case with the sponsor’s medical monitor and has provided a written action plan.
- 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

In the event that a patient is withdrawn from the study, every effort must be made by the investigator to document and report the reasons for withdrawal as thoroughly as possible. The reason(s) for withdrawal must be clearly reported on the appropriate page of the patient’s eCRF. An eCRF must be completed for any patient enrolled, and an End-of-Treatment reason must be recorded for any patient who is enrolled, regardless of whether they receive study drug.

If a patient is discontinued from the trial for any reason, every effort must be made to perform all End-of-Treatment and 30 Days After Last Dose assessments per the schedule of events (Table 1) (Parts 1 and 2 [dose escalation and expansion cohorts]) and Table 2 (Part 3 [extension cohort]). In the event that the patient fails to return for the necessary visit(s), an effort must be made to contact the patient to determine the reason, and this information should be recorded in the appropriate source record and reported as a deviation.

All patients who permanently discontinue the study drug will be followed for survival for at least 3 years after the last patient has enrolled. For patients who discontinue the study treatment due to a reason other than documented PD, additional tumor assessments should be documented, if available, until disease progression or start of another systemic anti-cancer therapy.
12.10 Study or Site Termination

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

- The discovery of a serious, unexpected, or unacceptable risk to subjects enrolled in the study
- The decision on the part of the sponsor to suspend or discontinue testing, evaluation, or development of the study drug
- Submission of knowingly false information from the research facility to the sponsor, medical monitor, or regulatory authorities
- Insufficient adherence to protocol requirements

Study termination and follow-up will be performed in compliance with the conditions set forth in the guidelines for Good Clinical Practice (GCP), International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

12.11 Sample Collection, Storage, and Shipping

All samples must be collected by appropriately trained individuals. Use of Universal Precautions is recommended when collecting any biological specimen. Specific instructions regarding the storage, handling, and shipment of plasma, serum, blood, and FFPE tumor specimens will be provided in the Study Reference Manual. FFPE tumor specimens are kept at room temperature. Freshly collected tumor specimens should be fixed with formalin and embedded in paraffin prior to shipment. Details of specific samples to be collected are provided in Section 12.1.

13 EFFICACY AND SAFETY ASSESSMENTS

13.1 Efficacy Assessments

Tumor response assessments will be evaluated by the investigator and/or by the IRC per RECIST v1.1 (see Appendix B). See Section 12.1 for the frequency of assessments. For patients who discontinue the study treatment due to a reason other than PD, additional tumor assessment should be documented, if available, until disease progression or start of another systemic anti-cancer therapy. Anti-tumor activity will be assessed by ORR using RECIST v1.1 or intracranial ORR (iORR) (Expansion Cohort 3). Secondary measures of efficacy will include: best target lesion response, duration of response, DCR, time to response, and PFS. OS will also be measured.

13.2 Safety Assessments

Safety assessments will include physical and laboratory examinations, vital signs and ECGs. AEs will be graded according to NCI CTCAE v4.0 (before Amendment 3) and NCI CTCAE v5.0 (after Amendment 3; see [18] and Study Reference Manual). Periodic meetings with study investigators will be held to assess safety data during the dose escalation phase.
All patients receiving at least 1 dose of TAK-788 will be considered evaluable for safety. The AE incidence rates, as well as the frequency of overall toxicity, categorized by toxicity Grades (severity), will be described. Listings of laboratory test results will also be generated, and descriptive statistics summarizing the changes in laboratory tests over time will be presented.

13.3 Pharmacokinetic Assessments

Blood samples will be collected at pre-specified time points (see Schedule of Events) to assess the plasma concentrations of TAK-788 and active metabolites (AP32960 and AP32914) following a single dose and multiple doses (steady state) of TAK-788, in the dose escalation cohorts. PK parameters, such as time of maximum concentration, maximum concentration, area under the concentration-time curve, clearance, volume of distribution, terminal half-life, and accumulation ratio will be estimated where possible.

PK evaluation will also be performed for the expansion cohorts to obtain cohort-specific PK at the recommended dose and frequency established in the dose escalation phase of the trial. PK sampling time points will be the same as the sampling time points in the dose escalation phase; however, adjustments may be made based on the PK findings in the dose escalation phase.

In the extension cohort, sparse plasma concentration data of TAK-788 and its active metabolites, AP32960 and AP32914, collected at pre-specified time points (see Schedule of Events) will contribute to population PK and exposure-response analyses.

Upon completion of bioanalysis of plasma samples for TAK-788 and metabolite drugs levels, leftover plasma samples may be used for exploratory evaluations (eg, metabolite profiling, etc). These data will not be reported in the final clinical study report (CSR).

Part 3: Extension Cohort

13.5 Patient-Reported Outcome Assessments (for Part 3 [Extension Cohort] Only)

Patient-reported outcomes will be collected by administering the following paper questionnaires: the EORTC QLQ-C30 (v3.0), the lung cancer-specific module (the EORTC QLQ-LC13, v3.0), the . 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. 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 [20]. 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 [21,22]. 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.

14 STUDY TREATMENT

14.1 Study Drug

TAK-788 is an investigational drug that will be administered only to eligible enrolled patients at qualified centers.

The Phase 2 expansion and extension cohorts will receive TAK-788 at the RP2D of 160 mg QD.
Patients will continue to be treated with TAK-788 until they experience PD that requires an alternate therapy in the opinion of the investigator, intolerable toxicity, or another discontinuation criterion (Section 12.9). Treatment may be continued after PD if, in the opinion of the investigator, the patient continues to experience clinical benefit.

14.2 Selection of the Starting Dose

The 28-day oral toxicity studies in rats and dogs support initiation of the first clinical trial at a starting oral dose of 5 mg/day. The rationale for selecting the starting dose of TAK-788 follows the guidance of an acceptable method for selecting the first dose of non-specific cytotoxic agents for a first-in-human trial in cancer patients [23,24]. This guidance recommends that the first-in-human trial begin with a dose that is 1/10 of the dose that is severely toxic to 10% of tested rodents (STD10) on a mg/m² basis, provided that this dose level is shown to be tolerated in a non-rodent species. If the non-rodent is the most sensitive species then 1/6 the non-rodent highest non-severely toxic dose (HNSTD) is considered an appropriate starting dose. In the 28-day rat and dog studies with TAK-788, the rat STD10 is 10 mg/kg/day and the dog HNSTD is 1 mg/kg/day. The rat STD10 translates to a dog dose of 3 mg/kg/day which exceeds the dog HNSTD of 1 mg/kg/day. The steady state mean (combined gender) AUClast of 681 h.ng/mL at the dog HNSTD of 1 mg/kg/day is 0.4x the steady state mean (combined gender) AUClast of 1745 h.ng/mL at the rat STD10 of 10 mg/kg/day. Therefore, the dog species is more sensitive to the toxicity of TAK-788 than the rat species based on both dose and exposure standpoints. The clinical starting dose is calculated to be 6.3 mg/day based on dog HNSTD. The proposed clinical starting dose is 5 mg/day.

14.2.1 Treatment Administration

TAK-788 succinate drug product will be administered orally. Study drug (TAK-788) will be self-administered by the patient. The starting dose will be 5 mg taken orally QD. 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 calories 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 card, 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 dosing diaries should be returned at the next available on-site clinic visit.

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 card. Under no circumstance should a patient repeat a dose or double-up doses.

14.2.2 Part 1: Dose Escalation

The dose escalation phase of the proposed phase 1/2 trial will employ sequential dose escalation of oral TAK-788 using a standard 3+3 design, starting at 5 mg administered orally QD, and increasing in increments until the MTD is identified. Figure 2 provides a schematic representation of the dose escalation phase of the study. The following guidelines are provided; however, decisions for dose escalation will be made in conference with the investigators and...
sponsor. Doses in between or higher than those shown in the following guidance may be explored.

Figure 2  Schematic of TAK-788 Phase 1/2 Trial Design – Dose Escalation Phase

Initially, 3 patients will be enrolled taking 5 mg of TAK-788 administered orally QD, and will be followed for 28 days. Increases of up to 100% over the previous dose level cohort will be employed until a Grade 2 drug-related toxicity of diarrhea or skin rash occurs, based on consideration of expected class effects for EGFR TKIs, or other DLTs are identified. Further dose escalation will involve increments of no more than 50% of the previous dose, depending on safety findings. Alternative dosing regimens may be administered based on PK findings for the initial patients. Should a modification of dosing levels be required, the dose escalation scheme will be altered by interpolating non-QD schedules into the initial escalation scheme.

Each dose escalation cohort will have a minimum of 3 patients enrolled and followed for 28 days. Increasing to the next dose level will depend on the safety findings of the previous cohorts. Expansion of a cohort from 3 to 6 patients will occur if 1 of 3 patients experiences a DLT at a given dose. If 1 or more patients experience a DLT in the additional 3 patients in a dose cohort (ie, for a total of ≥2 of 6 patients with a DLT), the dose level will be designated to have exceeded the MTD. If no patients experience a DLT in the additional 3 patients (ie, for a total of

Key: DLT=Dose-Limiting Toxicities, MTD=Maximum Tolerated Dose. RP2D=Recommended Phase 2 Dose. QD=once daily.
≤1 of 6 patients with a DLT), dose escalation will continue. Expansion of the cohort size may also occur at any dose to confirm safety, efficacy, and PK observations.

The maximum administered dose in the trial will likely exceed the MTD. Intermediate doses between the MTD and the next lower dose may be explored. Administration schedules for single or multiple dosing of TAK-788 in a given period or alternative schedules may be explored depending on PK findings and safety and tolerability data in continuous dosing cohorts.

### 14.2.2.1 Intra-patient Dose Escalation

Intra-patient dose escalation will be allowed according to the following scheme. All patients will have the option to increase dose while on the study if the following conditions are met: 1) the patient tolerated his/her starting dose without a DLT, 2) the Cycle 2 PK samples have been drawn per protocol, and 3) the proposed next dose level has been evaluated and it has been shown that it does not exceed the MTD.

### 14.2.2.2 Maximum Tolerated Dose (MTD)

The MTD is defined as the highest dose at which ≤1 of 6 evaluable patients experience a 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. The cohort may be expanded to better define the safety profile for confirmation of the MTD. The maximum administered dose in the trial will likely exceed the MTD. 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.

### 14.2.2.3 Dose-Limiting Toxicities (DLTs)

DLTs will be summarized by category (hematologic and non-hematologic) and by Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term. Standard AEs will be considered DLTs that count for the determination of the MTD of TAK-788. 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. Drug-related toxicities include any toxicity that is possibly, probably, or definitely drug related. Toxicity Grades will be defined by the NCI CTCAE v4.0 prior to Amendment 3 and by NCI CTCAE v5.0 following Amendment 3, if needed. 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 [ANC] <0.5 × 10⁹/L);
  - Prolonged Grade 4 neutropenia (≥7 days);
  - Neutropenic infection: ≥ Grade 3 neutropenia with ≥ Grade 3 infection;
iv. Thrombocytopenia ≥ Grade 3 with bleeding or Grade 4 without bleeding lasting ≥7 days

- Missed ≥25% of planned doses of TAK-788 over 28 days due to treatment-related AEs in the first cycle.

### 14.2.3 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.

Any medication, including those administered for therapy of symptoms considered to be associated with study drug administration, should be reported on the appropriate concomitant medication page of the patient’s eCRF. The symptoms should be reported on the AE page.

### 14.2.4 Dose Modification(s)

Dose delays or reductions will be implemented for patients who experience treatment-related AEs as indicated in the following section and in Table 3. 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 14.2.4.2 below. If toxicity requiring dose reduction occurs in the first dose cohort, discontinue therapy.

#### Table 3 Dose Modifications

<table>
<thead>
<tr>
<th>Toxicity Grade</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-Hematologic Toxicity</strong></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>Continue therapy at same dose level.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Continue therapy at same dose level. If symptoms are intolerable, recurrent, or not controlled by supportive care, withhold therapy until symptoms remit and reduce to next lower dose level.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Withhold therapy until toxicity is ≤ Grade 1 or has returned to baseline, then resume therapy. Therapy may be resumed at the same dose or at the next lower dose level, based on the investigator’s judgment.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>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.</td>
</tr>
<tr>
<td><strong>Hematologic Toxicity</strong></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>Continue therapy at same dose level.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Continue therapy at same dose level.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Withhold therapy until toxicity is ≤ Grade 2 or has returned to baseline, then resume therapy. Therapy may be resumed at the same dose or at the next lower dose level, based on the investigator’s judgment.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>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.</td>
</tr>
</tbody>
</table>
Further instructions for dose modification/management of diarrhea, asymptomatic lipase/amylase elevation, and pneumonitis can be found in Section 14.2.4.1.

**Table 4**  
TAK-788 Dose Reduction Schedule for Parts 2 and 3 (Expansion and Extension Phases)

<table>
<thead>
<tr>
<th>Dose Reduction Schedule</th>
<th>Dose Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dose</td>
<td>160 mg QD</td>
</tr>
<tr>
<td>First dose reduction</td>
<td>120 mg QD</td>
</tr>
<tr>
<td>Second dose reduction</td>
<td>80 mg QD</td>
</tr>
</tbody>
</table>

QD=once daily.

### 14.2.4.1 Management of Selected Treatment-Related Adverse Events

#### 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. 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.

#### 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.

#### 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.
14.2.4.2  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 escalation dose must not exceed the MTD, and the patient must have recovered from the AE. For patients who continue the treatment despite radiologic disease progression (as described in Section 12.9), the dose may be escalated to a higher dose that is determined not to exceed the MTD, following discussion with the sponsor.

14.2.5  Initiation of Part 2 (Expansion Phase) and Part 3 (Extension Cohort) Enrollment

The decision to proceed from the dose-escalation portion of the study and to open the expansion cohorts will depend on the establishment of the TAK-788 clinical safety profile. Enrollment in expansion cohorts will be dependent on observing evidence of disease response in the dose escalation cohort. Once the RP2D is identified, patients will be enrolled into the molecularly defined expansion cohorts comprising Part 2 of the study design (Figure 1). The expansion phase will include 7 additional histologically and molecularly defined cohorts, with Expansion Cohort 3 being limited to patients with active, measurable brain metastases (Figure 1). The dose and schedule for the expansion cohorts will be the RP2D and schedule determined in the dose escalation phase of the trial (160 mg QD). The enrollment of the Part 3 extension cohort will be initiated following establishment of early proof-of-concept. The dose and schedule for the extension cohort will be 160 mg QD.

14.3  Prior and Concomitant Treatment(s)/Therapy

History of prior cancer therapy will be recorded at screening, and concomitant cancer therapy will be recorded during the study on the appropriate eCRF for each patient.

Reasonable efforts will be made to collect information on all prior cancer therapy received by the patient (eg, surgeries, chemotherapy, radiotherapy, immunotherapy, biologics). The information must be obtained from the patient’s medical chart and recorded on the appropriate eCRF.

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

Concomitant medications for all ongoing medical history conditions or AEs must be reported from the date the informed consent is signed until at least the 30 Days After Last Dose assessments, and for all concomitant medications related to serious or study drug-related toxicities until the medication is no longer taken or until patient contact discontinues.

14.4  Prohibited Treatment(s)/Therapy

Once a patient has begun treatment, the following concurrent medications are prohibited:

• 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 (see Appendix D). Medications that prolong the QT interval, but are not known to be associated with Torsades de Pointes, should be avoided but are not prohibited;
- 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 inducers or inhibitors or strong inducers or inhibitors of the CYP3A family of Cytochromes P450 (see Appendix C), with the exception of nonsystemic use (eg, topical).
- Any illicit substance. Note: Medical use of cannabis is allowed, if it is legal where the patient resides and no alternative treatment is available, on the basis of case-by-case review and agreement by the medical monitor.

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.

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

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

Based on nonclinical in vitro data, TAK-788, AP32914, and AP32960 are not anticipated to inhibit CYP1A2-, CYP2C9-, CYP2C19-, or CYP2D6-mediated metabolism of coadministered drugs. Given the inhibition constant (K_i) 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 (22.3-2.51 μM [testosterone 6β-hydroxylation] and 19.7-1.98 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.

See also Section 15.3.1 for potential interaction between TAK-788 and CYP3A substrates, including hormonal contraceptives.

14.6 Treatment Compliance

Patients will be provided a diary card or equivalent in which the date and time of study drug administration will be recorded and complete instructions will be provided with the Study Reference Manual. Patients who forget to take or miss their dose (ie, >6 hours after scheduled time of administration) 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. The investigator is responsible for ensuring that the patient diary card(s) are accounted for and noted in source documentation.

14.7 Treatment(s) Supply

Upon receipt of clinical trial materials and/or study drug, the investigator or designee must verify that the shipment was received as stated on the clinical supply shipment form, enclosed within each shipment. The form is then returned to the clinical supply distributor as instructed on the form. If there are any discrepancies with the shipment, the sponsor should be contacted immediately (contact information is listed on the clinical supply shipment form). A copy of this form must be retained in the site files.
14.7.1 Formulation, Packaging, and Labeling

TAK-788 drug product is provided as 5 mg, 20 mg, and 40 mg capsules for oral dosing. The drug product is manufactured in accordance with cGMP. 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.

14.7.2 Treatment(s) Storage, Dispensing, and Accountability

The recommended storage condition for TAK-788 is controlled room temperature.

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’s initials, the patient’s study number, drug product strength, quantity dispensed with the corresponding lot number, and the initials of the person dispensing the drug. These logs are to be maintained by the study pharmacist in the pharmacy throughout the duration of the study and will be periodically verified by a representative of the sponsor.

Disruption to site visits due to the COVID-19 pandemic may require the site to use an alternative method for dispensing TAK-788 to ensure continuity of treatment. If allowed by country regulation/ethics committees, TAK-788 can be shipped DTP from the investigation site to the patient’s home address via courier if needed.

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.

14.7.2.1 Disposition of Used Supplies

All used bottles of study drug must be destroyed in an appropriate manner according to the standard practice at each study center. Destruction of such supplies will be documented, and a representative of the sponsor will verify disposition records.

During the trial and at termination, patients must return all unused study drug supplies, and the return of these unused study drug supplies must be recorded. Returned supplies must not be re-dispensed.

No other utilization of TAK-788 intended for use in this study is authorized by the sponsor. The principal investigator or his/her designee will be responsible for the appropriate handling and disposition of residual study drug. Each site is responsible for proper and careful destruction of study drug returned by patients.

14.7.2.2 Inventory of Unused Supplies

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

15  ADVERSE EVENT REPORTING

15.1  Adverse Events

15.1.1  Adverse Event Definition

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that may or may not have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product whether or not considered related to the medicinal product. Any worsening of a pre-existing condition that occurs after informed consent is also an AE.

Adverse Events include:

- Abnormal test findings, according to the following criteria:
  - Test results associated with accompanying symptoms that are considered clinically significant in the opinion of the investigator.
  - Selected asymptomatic laboratory values may also constitute AEs as defined by the NCI CTCAE.
  - Test results that require additional diagnostic testing (other than merely repeating an abnormal test) or medical/surgical intervention.
  - Test results that lead to a change in study drug dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
  - Test results considered to be an AE by the investigator or sponsor.

- Changes in physical examination findings

- Other untoward medical events, regardless of their relationship to the study drug, such as injury, events that require surgery, accidents, or apparently unrelated illnesses, and

- Hypersensitivity

Additionally, AEs may include signs or symptoms resulting from:

- Drug overdose (events occurring from a medication error or overdose of a product or products, whether accidental or intentional)

- Drug withdrawal

- Drug abuse

- Drug misuse

- Drug interactions

- Drug dependency
Exposure during breastfeeding

Exposure in utero

15.1.2 Performing Adverse Events Assessments

All observed or volunteered AEs, regardless of suspected causal relationship to the investigational product(s), will be reported, as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious AE (SAE; see Section 15.2), requiring immediate notification to the sponsor or its designated representative.

15.1.3 Reporting Period

All AEs (serious and non-serious) should be recorded on the AE eCRF for all patients beginning at the time of signing the informed consent form and concluding 30 days following the last dose of the assigned study drug in the study or the investigator/patient decision to discontinue treatment, whichever occurs later.

Once a patient is deemed a screen failure, AE collection is no longer required.

Any ongoing AEs (serious and non-serious) after the reporting period should be followed until they resolve to baseline, stabilize, or are considered to be chronic/irreversible.

SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the signing of informed consent through 30 days after administration of the last dose of study drug and recorded in the eCRF. After this period, only related SAEs must be reported to the Takeda Global Pharmacovigilance department or designee. SAEs should be monitored until they are resolved or are clearly determined to be due to a patient’s stable or chronic condition or intercurrent illness(es).

15.1.4 Adverse Event Severity

The severity of AEs will be assessed according to the CTCAE v4.0 (before Amendment 3) and CTCAE v5.0 (after Amendment 3; see [18] and the Study Reference Manual). If the AE is not defined in the CTCAE, the investigator will determine the severity of the AE based on the following definitions:

- **Mild (Grade 1)**: The AE is noticeable to the patient but does not interfere with routine activity;
- **Moderate (Grade 2)**: The AE interferes with routine activity but responds to symptomatic therapy or rest;
- **Severe (Grade 3)**: The AE significantly limits the patient’s ability to perform routine activities despite symptomatic therapy;
- **Life-Threatening (Grade 4)**: The patient is at immediate risk of death;
- **Death (Grade 5)**: The patient dies as a direct result of the complication or condition induced by the AE.
15.1.5  Causality

The investigator’s assessment of causality must be provided for all AEs (serious and non-serious). An investigator’s causality assessment is the determination of whether there exists a reasonable possibility that the study drug (ie, TAK-788) caused or contributed to the AE.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and on the SAE form and report such an assessment in accordance with the SAE reporting requirements.

The investigator will use medical consideration and use the following categories of causality to determine the relatedness of an AE with the study drug based on the following definitions. Not all criteria in each category of relatedness must be present.

In Parts 1 and 2 (dose escalation and expansion cohorts), the investigator will use the 5 following categories of relatedness to assess causality. In Part 3 (extension cohort), the 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?

Unrelated

Definitely Not Related (not drug related)

- The patient did not receive study drug,

OR

- The temporal sequence of the AE onset relative to the administration of the study drug is not reasonable, or

OR

- There is another obvious cause of the AE

Probably Not Related (not drug related)

- There is evidence of exposure to study drug
- There is another more likely cause of the AE
- De-challenge (if performed) is negative or ambiguous
- Re-challenge (if performed) is negative or ambiguous

Related

Possibly Related (drug related)

- There is evidence of exposure to study drug
- The temporal sequence of the AE onset relative to administration of the study drug is reasonable
- The AE could have been due to another equally likely cause
- De-challenge (if performed) is positive
**Probably Related (drug related)**
- There is evidence of exposure to study drug
- The temporal sequence of the AE onset relative to administration of the study drug is reasonable
- The AE is more likely explained by the study drug than by another cause

**Definitely Related (drug related)**
- There is evidence of exposure to study drug
- The temporal sequence of the AE onset relative to administration of the study drug is reasonable
- De-challenge is positive
- Re-challenge (if feasible) is positive
- The AE shows a pattern consistent with previous knowledge of the test drug or a test drug class

**15.1.6 Expectedness**
The expectedness of an SAE is assessed by the sponsor in the overall classification of SAEs for regulatory reportability. The Investigator Brochure will be used as the reference for determination of expectedness and risk assessment.

**15.2 Serious Adverse Events**
The definitions and reporting requirements of ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2A, will be followed.

**15.2.1 Serious Adverse Event Definition**
The investigator or the sponsor may determine the seriousness of an AE based on the criteria below.

An AE is considered an SAE if at least one of the following conditions applies:

- **Death**: An AE resulting in death within 30 days of the last dose of study drug administration. The cause of death or AE that resulted in a fatal outcome is the SAE.
- **Life-threatening AE**: An AE that places the patient, in the view of the investigator or the sponsor, at immediate risk of death from the event as it occurred (ie, this does not include an event that, had it occurred in a more severe form, might have caused death).
- **Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions**: Any substantial disruption of a person’s ability to conduct normal life functions.
- **Inpatient hospitalization or prolongation of existing hospitalization**: Hospitalization refers to admission of a patient into a hospital for any length of time.
- **A congenital anomaly/birth defect:** A fixed, permanent impairment established at or before birth.

- **Cancer:** Occurrence or diagnosis of a new cancer during the study is considered an SAE; a new cancer is a cancer that is histopathologically different from the cancer under study (ie, does not include metastatic or progressive disease).

- **Important medical event:** Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not result in death, be life-threatening, or require hospitalization. However, if it is determined that the event may jeopardize the patient and/or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse.

## 15.2.1.1 Progression of the Malignancy Under Study

Disease progression of the malignancy under study assessed by measurement of malignant lesions on radiographs or other methods should not be reported as an AE. However, worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section of the eCRF.

## 15.2.1.2 Hospitalizations

Adverse events (reported from clinical studies) that require hospitalization or prolongation of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a health care facility meets these criteria. Adverse events that require emergency room care that do not result in hospital admission are not SAEs unless assessed by the investigator to be an important medical event. Hospitalization does not include the following:

- Hospice facilities
- Respite care
- Skilled nursing facilities
- Nursing homes
- Routine emergency room admissions
- Same day surgeries (as outpatient/same day/ambulatory procedure)

Hospitalization or prolongation of hospitalization in the absence of a precipitating AE is not in itself an SAE. Examples include:
• Social admission (eg, patient has no place to sleep)
• Protocol-specified admission during a clinical study (eg, for a procedure required by the study protocol)
• Optional admission not associated with a precipitating AE (eg, for elective cosmetic surgery that was planned prior to study enrollment [appropriate documentation is required for these cases])
• Hospitalization or prolongation of hospitalization for scheduled therapy of the target malignancy of the study is not considered an SAE

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

15.2.2 Reporting Serious Adverse Events
Regardless of causality, the investigator or investigator’s designee must record all SAE information in the clinical trial database (eCRFs) within 24 hours after becoming aware of an SAE. In the event that the clinical trial database is not available, the SAE report must be sent to the sponsor’s Pharmacovigilance and Risk Management department or its designated representative within 24 hours using the provided form, and also entered into the clinical trial database when it becomes available. The 24-hour timeframe also applies to additional new information (follow-up) on previously reported SAEs.

Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the sponsor, if requested.

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

15.2.3 Information to be Provided by the Investigator for a Serious Adverse Event
The sponsor or designee will require all of the following information about the patient and the event:
• Investigator identification
• Patient identification code (eg, sex, age, or date of birth)
• Information on study drug (eg, start/stop date, dose, and frequency of study drug administered)
• Description of event

In addition to the above information, the sponsor will require the investigator’s assessment of the following:
• Severity of the SAE
• Relationship of the SAE to the study drug
• Outcome of the SAE
15.2.4 Follow-up Information on a Serious Adverse Event

The investigator may be asked to provide additional information for any event submitted, which may include a discharge summary or extracts from the medical record. Information provided about the event must be consistent with information recorded on the eCRFs where safety data may also be recorded (eg, AE CRF). The investigator is responsible for management of the patients through the course of the event. There should be routine follow-up through and including a minimum of 30 days after the last administration of study drug or the investigator/patient decision to discontinue treatment, whichever occurs later, in all patients in order to monitor for the occurrence of SAEs. If an SAE continues after the 30-day evaluation period, the patient must be followed until the event resolves or stabilizes without further involvement expected. The sponsor’s medical monitor may specify a longer period of time if required to assure the safety of the patient.

15.2.5 Expedited Reporting of Suspected Unexpected and Serious Adverse Reactions (SUSARs)

The sponsor is responsible for reporting suspected, unexpected, and serious adverse reactions (SUSARs) involving the study drug to all regulatory authorities and participating investigators in accordance with ICH Guidelines and/or local regulatory requirements, as applicable. In addition, the sponsor, or authorized designee, will be responsible for the submission of safety letters to applicable central independent ECs (IECs).

The sponsor will notify investigators of all reportable SAEs. This notification will be in the form of an expedited safety report. Upon receiving such notices, the investigator must review and retain the notice with other study-related documentation.

The investigator and Institutional Review Board (IRB)/IEC will determine whether the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

SUSARs and other significant safety issues reported from the investigational product development program will be reported by the sponsor or its designated representative, either as expedited safety reports and/or in aggregate reports, to the relevant competent health authorities in all concerned countries.

15.3 Other Safety Issues

15.3.1 CYP3A Substrates (Including Hormonal Contraceptives)

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 and other pregnane X receptor–inducible enzymes (eg, CYP2C9, CYP2C19) and transporters (eg, P-glycoprotein), including hormonal contraceptives, can result in decreased concentrations and loss of efficacy of these coadministered drugs.
15.3.2 Pregnancy and Breastfeeding

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 highly effective, nonhormonal contraception (ie, results in a low failure rate when used consistently and correctly), as specified below, during the dosing period and for a period of at least 30 days after the last dose of study drug. A pregnancy test will be performed on each pre-menopausal female patient of childbearing potential 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. If required by local standard medical practice, more frequent pregnancy testing is allowed.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, OR
- Surgically sterile, OR
- If they are of childbearing potential, agree to practice 1 highly effective, nonhormonal method and 1 additional effective (barrier) method of contraception (Table 5) at the same time, from the time of signing of the informed consent form through 30 days after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

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

- Agree to practice effective barrier contraception during the entire study treatment period and through 30 days after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
Table 5  **Highly Effective Methods of Contraception and Additional Effective (Barrier) Methods**

<table>
<thead>
<tr>
<th>Highly Effective Nonhormonal Methods</th>
<th>Additional Effective (Barrier Methods)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonhormonal intrauterine device (IUD)</td>
<td>Male or female condom with or without spermicide (female and male condoms should not be used together)</td>
</tr>
<tr>
<td>Bilateral tubal occlusion</td>
<td>Cap, diaphragm, or sponge with spermicide</td>
</tr>
<tr>
<td>Vasectomized sole sexual partner</td>
<td></td>
</tr>
</tbody>
</table>

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

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 sponsor’s Pharmacovigilance and Risk Management department or its designated representative.

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 study drug administration.

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

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

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 in the Study Reference Manual.

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

16.1 General Considerations

The dose escalation phase of this phase 1/2 trial will employ sequential dose escalation of oral TAK-788 using a standard 3+3 design, starting at 5 mg administered orally QD, and increasing in increments until the MTD is identified.

Descriptive statistics and analyses will be provided for each dose level and for patients combined across dose levels, where applicable.

Data from patients in the expansion phase cohorts will be summarized together with data from patients in the dose escalation cohorts, as appropriate.

Descriptive statistics (such as means, medians, standard deviations, and ranges for continuous data, and percentages for categorical data) will be used to summarize patient characteristics, treatment administration/compliance, efficacy, safety, and PK parameters. Data will also be displayed graphically, where appropriate.

Two-sided exact 95% binomial confidence intervals (CIs) will be computed for all binary efficacy endpoints.

The primary analysis for the extension cohort is planned to be conducted when all ongoing patients have completed their Cycle 6 disease assessment. Additional details of the analyses will be provided in the statistical analysis plan.

16.2 Analysis Populations

Full analysis set: All patients who receive at least 1 dose of TAK-788 will be included in the full analysis set. Primary analyses of efficacy and safety will be based on the full analysis set.

Per-protocol population: The per-protocol population will include previously treated patients dosed at 160 mg with EGFR exon 20 insertion mutations who have measurable disease at baseline per the IRC and have at least 2 post-baseline disease assessments unless the reason for having fewer than 2 disease assessments is patient death or study drug discontinuation due to toxicity or documented PD.

16.3 Study Endpoints

16.3.1 Primary Endpoints

Part 1: Dose Escalation Cohorts

The primary endpoint of the dose escalation component of the study is the RP2D of orally administered TAK-788.

Part 2: Expansion Cohorts

The primary endpoint of the expansion cohorts is the investigator-assessed confirmed ORR (using RECIST v1.1), except for Expansion Cohort 3, in which iORR (as assessed by the IRC) will be the primary endpoint, and Expansion Cohort 6, in which confirmed ORR (as assessed by the IRC, using RECIST v1.1) will be the primary endpoint.
Part 3: Extension Cohort
The primary endpoint of the extension cohort is confirmed ORR, as assessed by the IRC, per RECIST v1.1.

16.3.2 Secondary Endpoints

Part 1: Dose Escalation Cohorts
Secondary endpoints of the dose escalation component of the study include:
1. DLTs and MTD of orally administered TAK-788
2. Safety profile of orally administered TAK-788
3. Plasma PK parameters of TAK-788 and its active metabolites (including, but not limited to, AP32960 and AP32914) after a single oral dose and at steady state after multiple oral doses

Part 2: Expansion Cohorts
Secondary endpoints of the expansion cohort component of the study include:
1. Safety profile of orally administered TAK-788
2. 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
3. Efficacy assessments including: confirmed ORR as assessed by an IRC, per RECIST v1.1 (except Expansion Cohort 6); best overall response, best target lesion response, duration of response, DCR, time to response, and PFS, as assessed by the investigator and IRC; and OS
   a. For Expansion Cohort 3, additional efficacy assessments include: intracranial duration of response (iDOR) and intracranial PFS (iPFS)
   b. For Expansion Cohort 6, secondary efficacy assessments will include confirmed ORR as assessed by the investigator, per RECIST v1.1.

Part 3: Extension Cohorts
Secondary endpoints of the extension cohort component of the study include:
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 CR, PR, or SD), 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 HRQoL with the EORTC QLQ-C30 and QLQ-LC13
16.3.3 Safety Endpoints
Safety endpoints for the extension cohort include the following:
1. Adverse events
2. Laboratory values
3. Vital signs
4. Physical examination findings

16.3.4 Other Endpoints

Part 3: Extension Cohort

16.3.5 Definitions of Efficacy Endpoints
- Confirmed ORR will be defined as the proportion of patients achieving a best confirmed response of CR or PR. Confirmed responses are responses that persist on repeat imaging ≥4 weeks after initial response.
- Duration of response will be defined as the time interval from the time that the measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that PD is objectively documented.
DCR will be defined as the percentage of patients who have achieved CR, PR, or SD (in the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks) after the initiation of study treatment.

PFS will be defined as the interval from the first dose of TAK-788 until the first date at which the criteria for disease progression according to RECIST v1.1 are met or death. Patients who do not progress or die will be censored at the last disease assessment.

OS will be defined as the interval from the first dose of TAK-788 until death. Patients who do not die will be censored at last contact date.

Time to response will be defined as the time interval from the date of the first dose of TAK-788 until the initial observation of CR or PR.

iORR will be defined as the proportion of the patients who have achieved CR or PR in the CNS, as assessed by the IRC, after the first dose of TAK-788 in patients with brain metastases at baseline.

iPFS will be defined as the time interval from the date of the first dose of TAK-788 until the first date at which CNS disease progression is objectively documented, or death due to any cause, whichever occurs first, in patients with brain metastases either at baseline or after the first dose of TAK-788.

iDOR will be defined as the time interval from the time that the measurement criteria are first met for CR/PR in the CNS (whichever is first recorded) until the first date that CNS disease progression is objectively documented.

ORR, time to response, duration of response, DCR, and PFS will be assessed by both the IRC and the investigator. iORR, iPFS, and iDOR will be assessed by the IRC only.

Censoring for time-to-event efficacy endpoints will be detailed in the statistical analysis plan.

16.4 Determination of Sample Size

16.4.1 Parts 1 and 2: Dose Escalation and Expansion Cohorts

The purpose of this phase 1/2 trial is to determine the RP2D and MTD as well as evaluate the safety, tolerability, and anti-tumor activity of oral TAK-788 in patients with advanced NSCLC and other solid tumors. The sample size is determined based on clinical rather than statistical considerations. The number of patients in this trial is consistent with phase 1 dose finding studies; the histologically and molecularly defined expansion cohorts will facilitate obtaining estimates of clinical activity. With this design, the estimate of the rate of DLT at the MTD is in the range of 0.17 to 0.26. The estimate of the rate of DLT at the highest dose, which is 1 step above the MTD, is 0.33 [19].

16.4.2 Part 3: Extension Cohort

The purpose of the extension cohort in the phase 2 part of this study is to determine the confirmed ORR of orally administered TAK-788 at 160 mg QD in patients with NSCLC with EGFR exon 20 insertion mutations. Approximately 91 patients with NSCLC with tumors harboring EGFR exon 20 insertion mutations on the basis of a local
test will be enrolled to include approximately 73 patients with centrally confirmed EGFR exon 20 insertion mutations, assuming a 20% discrepancy between the documented mutation status by local testing results and central testing using an analytically validated central test.

16.5 Efficacy Analysis

16.5.1 Part 2: Efficacy Analyses in Expansion Cohorts

For the expansion cohorts, estimates of clinical activity, including confirmed ORR, time to response, duration of response, best target lesion response, best overall response, DCR, and PFS, will be determined using RECIST v1.1 (as determined by the investigator and by IRC). iORR, iPFS, and iDOR will be determined by the IRC. When appropriate, data from patients in the expansion cohorts will be summarized together with data from patients in the dose escalation phase.

For each cohort and tumor type, the investigator and IRC-assessed best overall response and confirmed overall response (CR, PR, SD, or PD according to RECIST – see Appendix B) for each patient with measurable disease who received at least 1 dose of study medication will be listed, and exact two-sided 95% CIs for the investigator and IRC-assessed confirmed ORR will be calculated based on the binomial distribution. Duration of response (in responders), iDOR, PFS, iPFS, and OS will be analyzed using the Kaplan-Meier method [25]. PFS and iPFS rates at 6 months and 12 months will be computed along with CIs. The OS rates at 12 and 24 months and associated CIs will be computed. Best target lesion response will be displayed using a “waterfall” plot. Descriptive statistics will be used to summarize time to response in responders and time on treatment. For Expansion Cohort 6, two-sided exact 95% binomial CIs will be computed for all binary secondary endpoints, including confirmed ORR as assessed by the investigator and DCR as assessed by the IRC and the investigator. All patients receiving at least 1 dose of TAK-788 will be considered evaluable for efficacy.

16.5.2 Part 3: Primary Efficacy Endpoint Analyses in the Extension Cohort

The best response (CR, PR, SD, or PD) according to RECIST v1.1 will be derived for each eligible patient. Patients with no measurable disease at baseline or no adequate post-baseline response assessment will be included as nonresponders. Confirmed ORR is calculated as the proportion of treated patients who are confirmed to have achieved CR or PR after the initiation of study treatment. Confirmed responses are those that persist on repeat imaging at least 4 weeks after initial response.
The primary endpoint of confirmed ORR, as assessed by the IRC, will be tested using exact methods in the full analysis set. Exact two-sided 95% CIs for the confirmed ORR will be calculated based on the binomial distribution.

Best percent change in the sum of target lesion diameters will be displayed using a “waterfall” plot. Supportive sensitivity analyses will be performed for ORR assessed by the IRC in the per-protocol population and using all responses (ie, including unconfirmed responses).

16.5.3 Part 3: Secondary Efficacy Endpoint Analyses in the Extension Cohort

Confirmed ORR assessed by the investigator in the full analysis set and the per-protocol population will be analyzed to assess the robustness of the primary analysis of the primary endpoint.

DCR assessed by the investigator and the IRC in the full analysis set and the per-protocol population and the exact two-sided 95% binomial 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 two-sided 95% CIs will be computed using Kaplan-Meier method [25] in the full analysis set and the per-protocol population. The PFS rates, OS rates, and duration of response rates at 12 and 24 months and the associated two-sided 95% CIs will be computed using the Kaplan-Meier method. Time to response will be summarized only for responders using descriptive statistics.

16.5.5 Data Handling Rules for Efficacy Endpoint Analyses

A patient will be considered not evaluable for response at a protocol-specified time point if no imaging/measurement is done or if only a subset of lesion measurements is obtained unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. A patient will be considered to have a response if
the criteria for response have been met at the protocol-specified time points immediately before and after the time point where response was not evaluable.

All patients will be assigned to 1 of the following best-response categories: CR, PR, SD, PD, or not evaluable. All patients whose best response is not CR or PR will be considered nonresponders in the calculation of ORR. Detailed data handling rules for efficacy outcomes as well as sensitivity analyses will be provided in the statistical analysis plan.

16.6 Safety Analysis

Safety assessments will include physical and laboratory examinations, vital signs, and ECGs. Adverse events will be graded according to the NCI CTCAE v4.0 (before Amendment 3) and NCI CTCAE v5.0 (after Amendment 3). Periodic meetings with study investigators will be held to assess safety data throughout the trial.

All patients receiving at least 1 dose of TAK-788 will be considered evaluable for safety. The AE incidence rates, as well as the frequency of occurrence of overall toxicity, categorized by toxicity Grades (severity), will be described. Listings of laboratory test results will also be generated, and descriptive statistics summarizing the changes in laboratory tests over time will be presented.

16.6.1 Pharmacokinetic Analysis

Parts 1 and 2: Dose Escalation and Expansion Cohorts

The following PK parameters for TAK-788 and its active metabolites, AP32960 and AP32914, will include (but are not limited to) the following for patients enrolled in the dose escalation and expansion cohorts.

Following a single oral dose in the dose escalation and expansion cohorts:

- $C_{\text{max}}$
- Time of first occurrence of $C_{\text{max}}$ ($t_{\text{max}}$)
- Area under the concentration-time curve (AUC)
  - from time zero to 24 hours (AUC$_{24}$)
  - from time zero to time $t$ (AUC$_t$)
- Dose proportionality for $C_{\text{max}}$ and AUC

Following multiple oral doses (steady state) in the dose escalation and expansion cohorts:

- Maximum observed concentration during a dosing interval, at steady state ($C_{\text{max,ss}}$)
- Time of first occurrence $C_{\text{max,ss}}$ ($t_{\text{max,ss}}$)
- AUC
  - AUC$_{24}$
  - AUC$_t$
- Apparent clearance at steady state (CL/F$_{ss}$)
Volume of distribution at steady state ($V_z/F_{ss}$)

Accumulation ratio based on AUC during a dosing interval ($R_{ac(AUC)}$)

Accumulation ratio based on $C_{max}$ ($R_{ac(Cmax)}$)

Effective half-life ($t_{1/2eff}$)

Dose proportionality for $C_{max}$ and AUC

### Part 3: Extension Cohort

The sparse plasma concentration data of TAK-788 and its active metabolites, AP32960 and AP32914, collected in patients in the extension cohort will be pooled with data from the dose escalation and expansion cohorts to contribute to population PK analyses. These analyses may additionally include data collected in other TAK-788 clinical studies. 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.

#### 16.6.2 Parts 1 and 2: QTcF Analysis for Dose Escalation and Expansion Cohorts

Descriptive statistics of maximum QTcF and change from baseline will be calculated following the ICH-E14 guidelines: the proportion of treated patients with at least 1 on-drug QTcF value >450 ms, 480 ms, and 500 ms; and the proportion of treated patients with a maximum change in QTcF from baseline >30 ms and >60 ms. The Fridericia correction (QTcF) will be used throughout. The PK and ECG data collected in this study will contribute to analysis of concentration-effect (such as QTc change from baseline) relationships using linear mixed effects models.

#### 16.7 Part 3: Patient-Reported Outcome Data Analysis

The main patient-reported outcomes endpoints of interest for the extension cohort 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 [26] 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.

The percentage of compliance for EORTC QLQ-C30, QLQ-LC13, questionnaires will be summarized over time.

Questionnaires administered after other assessments and procedures at a visit or outside of scheduled visits will be flagged for potential exclusion.

More details will be provided in the statistical analysis plan.
16.8 **Part 3: Interim Analysis and Criteria for Early Termination**

A futility analysis will be planned for the primary endpoint for the extension cohort when approximately 20 patients have completed their Cycle 4 disease assessment. This criterion requires a minimum of 3 responders (confirmed and unconfirmed) out of 20 patients to pass the futility check.

16.9 **Protocol Deviations/Violations**

To be protocol-compliant, a patient must not have any major protocol deviations during the study period. Protocol deviations will be identified prior to database lock and will be listed by treatment group in the clinical study report.

17 **QUALITY CONTROL AND QUALITY ASSURANCE**

The sponsor performs quality control and assurance checks on all clinical studies that it sponsors. Before enrolling any patients into this study, the sponsor personnel or its designee and the investigator will review the protocol, the Investigator’s Brochure, the eCRFs and instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AEs. A qualified representative of the sponsor will monitor the conduct of the study by visiting the site and by contacting the site by telephone. During the visits, information recorded in the eCRFs will be verified against source documents. The sponsor’s medical monitor will review the data for safety information. The sponsor’s clinical data associates or designees will review the data for completeness and logical consistency. Additionally, the sponsor’s clinical data associates will use automated validation programs to help identify missing data, selected protocol violations, out-of-range data, and other data inconsistencies. Requests for data clarification or correction will be added to the electronic database and reviewed by the investigational site for resolution. The sponsor may visit the investigational site and perform a quality check of the eCRFs against source documents.

17.1 **Investigators and Study Administrative Structure**

The investigator must provide the sponsor with the following documents BEFORE enrolling any patients:

- An executed Clinical Trial Agreement,
- Completed and signed FDA Form 1572 or appropriate statement of investigator,
- Disclosure of financial interests in the sponsor or the sponsor’s products (as defined in 21 Code of Federal Regulations [CFR] part 54),
- Principal investigator’s Curriculum Vitae,
- IRB/EC approval of the protocol, and
- IRB/EC approved informed consent form.

If any investigator retires, relocates, or otherwise withdraws from conducting the study, the responsibility for maintaining records may be transferred to another person (sponsor, IRB/EC, or other investigators) who accepts the responsibility. The sponsor must be notified in writing and
must agree to the change. An updated FDA Form 1572 will be filed with the sponsor for any changes in study personnel reported in the current FDA Form 1572, and a disclosure of any financial interests in the sponsor or the sponsor’s products (as defined in 21 CFR part 54) will be required of any individual assuming the investigator’s responsibilities.

17.2 Study Monitoring

This study will be monitored by representatives of the sponsor. Site visits are made before the study begins, at regular intervals during the study, and at the study closeout. Communication by telephone, mail, and e-mail may be used, as needed, to supplement site visits. The investigator and study personnel will cooperate with the sponsor, provide all appropriate documentation, and be available to discuss the study. The purpose of the site visits is to verify:

- Adherence to the protocol (the investigator should document and explain any deviation from the approved protocol).
- The completeness and accuracy of the eCRFs and the dispensing and inventory record (adequate time and space for these visits should be allocated by the investigator).
- Compliance with regulations (the verification will require comparison of the source documents to the eCRFs).
- In the event a monitor cannot visit the site in a timely manner due to the COVID-19 pandemic, alternative monitoring approaches such as remote source data verification or telephone contact may be used to ensure data quality and integrity and maintain patient safety. Alternative monitoring approaches should be used only where allowed by applicable local regulations and permitted by the IRB/IEC.

18 ETHICAL CONDUCT 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 E. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities. Any significant change in the study protocol will require an amendment, which will be submitted to competent authorities and IRB/IEC for review and approval per applicable guidance and regulations.

Nothing in this protocol or the regulations is intended to limit the authority of a physician to provide emergency medical care under applicable regulations. In addition, the investigator should be aware that some regulations require that he/she permit regulatory agencies to conduct inspections and review records pertaining to this clinical investigation.

18.1 Institutional Review Board or Ethics Committee Approval

The protocol and the informed consent document must have the initial and at least annual or bi-annual (when required) approval of an IRB/IEC. The signed IRB/IEC approval letter must identify the documents approved (ie, list the investigator’s name, the protocol number and title, the date of the protocol and informed consent document, and the date of approval of the protocol.
and the informed consent document). Any advertisements used to recruit patients should also be reviewed by the IRB/IEC. The sponsor will not ship clinical supplies until a signed approval letter from the IRB/IEC has been received and a Clinical Trial Agreement has been signed by the sponsor and the clinical site.

18.2 Patient Information and Consent

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject’s personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, and the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

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

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. If the subject is not capable of rendering adequate written informed consent, then the subject’s legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject’s legally acceptable representative, must be given ample opportunity to (1) inquire about details of the study and (2) decide whether to participate in the study. If the subject, or the subject’s legally acceptable representative, determines that he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject’s legally acceptable representative, at the time of consent and before the subject enters into the study. The subject or the subject’s legally acceptable representative should be instructed to sign using their legal names, not nicknames, using a ballpoint pen with either blue or black ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and before the subject enters into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator’s site file. The investigator must document the date the subject signs the informed consent in the subject’s
medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject. All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject’s legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject’s medical record, and the subject should receive a copy of the revised informed consent form.

18.3 Patient Confidentiality

The sponsor and designees affirm and uphold the principle of the subject’s right to protection against invasion of privacy. Throughout this study, a subject’s source data will be linked to the sponsor’s clinical study database or documentation only via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject’s unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee’s monitor, representatives from any regulatory authority (eg, US FDA, United Kingdom Medicines and Healthcare products Regulatory Agency, Japan Pharmaceuticals and Medical Devices Agency), the sponsor’s designated auditors, and the appropriate IRBs and IECs to review the subject’s original medical records (source data or documents) including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject’s study participation, and autopsy reports. Access to a subject’s original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 18.2).

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.

All unpublished information that the sponsor gives to the investigator, and all information generated in connection with the study, shall be kept confidential and shall not be disclosed to a third party without the prior written consent of the sponsor or published prior to the sponsor’s review in accordance with the terms of the Clinical Trial Agreement. When the sponsor generates reports for presentations to regulatory agencies, one or more of the investigators who have contributed significantly to the study will be asked to endorse the final report. The endorsement is required by some regulatory agencies. The investigator shall not make a patent application based on the results of this study and shall not assist any third party in making such an application without the written authorization of the sponsor.

18.4 Study Committees

18.4.1 Parts 2 and 3: Independent Review Committee

A central IRC will evaluate all images collected during the study from patients enrolled in the Phase 2 expansion and extension cohorts, for all IRC-assessed endpoints. An IRC charter defines the procedures used by the committee.
18.4.2 Part 3: Data Monitoring Committee (for Extension Cohort)

An independent Data Monitoring Committee (DMC), consisting of 3 to 5 members not associated with the conduct of the study and/or the sponsor with the exception of the compensation to DMC members related to their activities, will be established for this study. The DMC members will be a multidisciplinary group that will include at least 2 oncologists with extensive experience in clinical study conduct and a biostatistician with substantial experience in the DMC process. The committee will perform data review quarterly and meet at least twice yearly until the final analysis has been performed, as specified in the protocol. Ad hoc DMC meetings may also be held if a significant issue should arise.

The DMC will be responsible for evaluating the results of safety analyses and making recommendations to the sponsor. Efficacy data can also be requested, if needed, to evaluate risk/benefit before making a recommendation. The DMC will operate under the DMC charter, which specifies the data to be included in each review, rules related to study modification, and protection of the integrity of the data. At each meeting, the DMC will make recommendations to either continue the study unchanged, to modify the study, or to discontinue the study. The DMC will communicate the recommendations to the sponsor. The final decision to act on the DMC recommendations will be made by the sponsor in consultation with the Study Steering Committee.

18.4.3 Part 3: Study Steering Committee (for Extension Cohort)

A steering committee will be established for the study. 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.

19 DATA HANDLING AND RECORD KEEPING

19.1 Case Report Forms and Study Records

Study-specific eCRFs will be made available to the investigative site. Study data, contained in source documentation, will be entered into the eCRFs for all patients who sign informed consent. All pertinent data records are to be submitted to the sponsor during and/or at completion or termination of the study.

19.2 Access to Source Documentation

The sponsor (or designee) will be permitted to review the subject’s medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for
authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

19.3 Retention of Data

Study documents (including correspondence related to this clinical study, patient records, source documents, eCRFs, study drug inventory records, and IRB/IEC and sponsor correspondence pertaining to the study, unique patient, laboratory, and study drug inventory records relating to the study) should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or planned marketing applications in an ICH region (that is at least 15 years or at least 2 years have elapsed since the formal discontinuation of clinical development of the product). Study documents should be retained for a longer period if required by applicable regulatory requirements or by agreement with the sponsor. Thereafter, records will not be destroyed without giving the sponsor prior written notice and the opportunity to further store such records, at the sponsor’s cost and expense.

19.4 Termination of Study

The sponsor may terminate the study at a study site or in its totality at any time for any of the following reasons:

- Failure to enroll patients
- Protocol violations
- Inaccurate or incomplete data
- Unsafe or unethical practices
- Questionable safety of the study drug
- Suspected lack of efficacy of the study drug
- Administrative decision

In the event of the termination of the study by either the sponsor or an investigator:

- The investigator will return all related study materials to the sponsor.
- A written statement describing why the study was terminated prematurely will be provided by either the sponsor or the investigator.

20 FINANCING AND INSURANCE

A clinical study agreement will be signed by the investigator (and/or, as appropriate, the hospital administrative representative) and the sponsor prior to the start of the study, outlining overall sponsor and investigator responsibilities in relation to the study. Financial remuneration will cover the cost per included patient, based on the calculated costs of performing the study assessments in accordance with the protocol, and the specified terms of payment will be described in the contract. The contract should describe whether costs for pharmacy, laboratory, and other protocol-required services are being paid directly or indirectly. Prior to the start of the study, investigators and sub-investigators will release sufficient and accurate information that permits the sponsor or sponsor-designated agent to determine that an investigator has no personal

Amendment 6 02 September 2020 Page 100 of 123
or professional financial incentive regarding the future approval or non-approval of the study drug that his/her research might be biased by such financial incentives. The financial information is exclusive of agreements directly related to fees associated with the study being conducted. All information provided will be regarded as strictly confidential and will only be disclosed to the respective regulatory authority.

21 PUBLICATION AND DISCLOSURE POLICY

The investigator must notify the IRB/IEC of the conclusion of the clinical study. This report should be made within 3 months of the completion or termination of the study. The final report sent to the IRB/IEC should also be sent to the sponsor and, along with the completed eCRFs, constitutes the final summary to the sponsor, thereby fulfilling the investigator’s regulatory responsibility.

The Declaration of Helsinki states that every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject (wma.net [accessed 12 Oct 2015]). Section 801 of the FDA Amendments Act mandates the registration with ClinicalTrials.gov of certain clinical studies of drugs (including biological products) and medical devices subject to FDA regulations for any disease or condition. The International Committee of Medical Journal Editors (ICMJE) requires study registration as a condition for publication of research results generated by a clinical study (icmje.org [Accessed: 13 January 2014]). In addition, the EMA requires that clinical studies conducted in the European Union and other countries under their regulatory authority be registered (clinicaltrialsregister.eu/ [Accessed: 13 January 2014]).

The institution and principal investigator acknowledge that the study is a multicenter study and, as such, agree that they will not publish a publication, abstract, poster, or other disclosures (“Publication”) before a combined paper that identifies all the sites that participated in the study (“Multi-Center Publication”) is published. If the Multicenter Publication has not been completed within 1 year from the date of the completion, termination, or abandonment of the multicenter study, the institution may publish or present its individual results in accordance with the provisions stated below.

In order to balance the institution’s right to publish with the sponsor’s proprietary interests, the institution will submit to the sponsor material intended for publication, abstracts, posters, and other disclosures (“Proposed Disclosures”) at least 45 days prior to submitting for publication or other disclosure to allow for expeditious review by the sponsor. If the sponsor believes that any Proposed Disclosure contains any information relating to any patentable invention, the disclosure of such Proposed Disclosure shall be delayed for up to 60 days from the date the sponsor receives the Proposed Disclosure to permit the sponsor to file patent applications. If the sponsor believes that any Proposed Disclosure contains Confidential Information, the sponsor shall have the right to require that the institution delete any reference to Confidential Information, excluding the results of the study or other Permitted Research. If the institution and principal investigator choose not to publish, the sponsor reserves the right to publish the results of the study, and, if appropriate, to include its medical staff in the author list of such publication in accordance with academic publication standards.

Subject to applicable copyright law, if an institution and/or principal investigator publishes results of the study, institution and/or principal investigator hereby grants the sponsor an
irrevocable, royalty-free license to make and distribute copies of such publication under any copyright privileges that the institution and/or principal investigator may have.
22 REFERENCES


6. TAGRISSO (osimertinib) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP, Apr 2018.


## Appendix A  Eastern Cooperative Oncology Group Performance Status

<table>
<thead>
<tr>
<th>ECOG Performance Status*</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>

*As published in Oken et al [27].
Appendix B  Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1)

Note: These criteria are adapted from Eisenhauer et al [28].

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

<table>
<thead>
<tr>
<th>Complete Response (CR)</th>
<th>Partial Response (PR)</th>
<th>Progressive Disease (PD)</th>
<th>Stable Disease (SD)</th>
<th>Non-evaluable (NE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Disappearance of all extranodal target lesions.</td>
<td>• At least a 30% decrease in the SLD of target lesions, taking as reference the baseline sum diameters</td>
<td>• SLD increased by at least 20% from the smallest value on study (including baseline, if that is the smallest)</td>
<td>• Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD</td>
<td>• 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)</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Target Lesions</th>
<th>Non-Target Lesions</th>
<th>New Lesions</th>
<th>Overall Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>CR</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>CR</td>
<td>Non-CR/Non-PD</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>CR</td>
<td>NE</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>PR</td>
<td>Non-PD or NE</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>SD</td>
<td>Non-PD or NE</td>
<td>No</td>
<td>SD</td>
</tr>
<tr>
<td>Not all evaluated</td>
<td>Non-PD</td>
<td>No</td>
<td>NE</td>
</tr>
<tr>
<td>PD</td>
<td>Any</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>PD</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>Yes</td>
<td>PD</td>
</tr>
</tbody>
</table>

NE=Not Evaluatable
### Appendix C  Drugs That Interact With the CYP3A Family of Cytochromes P450

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

<table>
<thead>
<tr>
<th>Moderate CYP3A Inducers&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>bosentan</td>
</tr>
<tr>
<td>efavirenz</td>
</tr>
<tr>
<td>etravirine</td>
</tr>
<tr>
<td>phenobarbital</td>
</tr>
<tr>
<td>primidone</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Strong CYP3A Inducers&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>apalutamide</td>
</tr>
<tr>
<td>carbamazepine</td>
</tr>
<tr>
<td>enzalutamide</td>
</tr>
<tr>
<td>mitotane</td>
</tr>
<tr>
<td>phenytoin</td>
</tr>
<tr>
<td>rifampin</td>
</tr>
<tr>
<td>St John’s wort</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Moderate CYP3A Inhibitors&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>aprepitant</td>
</tr>
<tr>
<td>ciprofloxacin</td>
</tr>
<tr>
<td>conivaptan</td>
</tr>
<tr>
<td>crizotinib</td>
</tr>
<tr>
<td>cyclosporine</td>
</tr>
<tr>
<td>diltiazem</td>
</tr>
<tr>
<td>dronedarone</td>
</tr>
<tr>
<td>erythromycin</td>
</tr>
<tr>
<td>fluconazole</td>
</tr>
<tr>
<td>fluvoxamine</td>
</tr>
<tr>
<td>imatinib</td>
</tr>
<tr>
<td>tofisopam</td>
</tr>
<tr>
<td><strong>verapamil</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Strong CYP3A Inhibitors&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>boceprevir</td>
</tr>
<tr>
<td>clarithromycin</td>
</tr>
<tr>
<td>cobicistat</td>
</tr>
<tr>
<td>danoprevir and ritonavir</td>
</tr>
<tr>
<td>elvitegravir and ritonavir</td>
</tr>
<tr>
<td>grapefruit juice</td>
</tr>
<tr>
<td>idelalisib</td>
</tr>
<tr>
<td>indinavir and ritonavir</td>
</tr>
<tr>
<td>itraconazole</td>
</tr>
<tr>
<td>ketoconazole</td>
</tr>
<tr>
<td>lopinavir and ritonavir</td>
</tr>
<tr>
<td>nefazodone</td>
</tr>
<tr>
<td>nelfinavir</td>
</tr>
<tr>
<td>paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)</td>
</tr>
<tr>
<td>posaconazole</td>
</tr>
<tr>
<td>ritonavir</td>
</tr>
<tr>
<td>saquinavir and ritonavir</td>
</tr>
<tr>
<td>telaprevir</td>
</tr>
</tbody>
</table>
telithromycin
tipranavir and ritonavir
troleandomycin
voriconazole

CYP=cytochrome P450.
This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to strongly or moderately modulate CYP3A activity. Appropriate medical judgment is required. Please contact the sponsor with any queries.
Appendix E Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the Statement of Investigator (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

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

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. Ensure that study-related procedures, including study-specific (nonroutine/nonstandard panel) screening assessments, are NOT performed on potential subjects before the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. Obtain valid informed consent from each subject who participates in the study and document the date of consent in the subject’s medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject’s personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject’s legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing
application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.

12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor. This responsibility lies on the appropriate individual, designated by the site in Japan.

13. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.
### ELECTRONIC SIGNATURES

<table>
<thead>
<tr>
<th>Signed by</th>
<th>Meaning of Signature</th>
<th>Server Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPD</td>
<td>Biostatistics Approval</td>
<td>02-Sep-2020 19:03 UTC</td>
</tr>
<tr>
<td></td>
<td>Clinical Approval</td>
<td>02-Sep-2020 19:03 UTC</td>
</tr>
<tr>
<td></td>
<td>Clinical Pharmacology Approval</td>
<td>02-Sep-2020 23:09 UTC</td>
</tr>
</tbody>
</table>