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

NCT Number: NCT03807778

Statistical analysis plan Approve Date: 14-JAN-2022

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

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

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

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

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-788-1003

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

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

Version: 3

Date: 14 Jan 2022

Prepared by:

[redacted]

Based on:

Protocol Version: Amendment 05

Protocol Date: 27 July 2020

1.1 Approval Signatures

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

2.0 TABLE OF CONTENTS

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC24	area under the concentration time curve from time 0 to 24 hours
AUC24,ss	area under the concentration time curve from time 0 to 24 hours, at steady state
AUClast	area under the concentration-time curve from time 0 to time of the last quantifiable concentration
β-hCG	beta-human chorionic gonadotropin
BLRM	Bayesian logistic regression model
CI	confidence interval
CL/Fss	apparent clearance at steady state
Cmax	maximum observed concentration
Cmax,ss	maximum observed concentration during a dosing interval, at steady state
CNS	central nervous system
CR	complete response
CRO	contract research organization
CSF	cerebrospinal fluid
CSR	clinical study report
CT	computed tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CxDx	Cycle x Day x
CYP	cytochrome P450
DCR	disease control rate
DDI	drug-drug interaction
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
EOT	end of treatment
EWOC	Escalation With Overdose Control
FAS	full analysis set
FDA	Food and Drug Administration (United States)
FFPE	formalin fixed paraffin embedded
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GM-CSF	granulocyte macrophage-colony stimulating factor

HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2	human epidermal growth factor 2
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
IC50	50% inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
ILD	interstitial lung disease
IRB	Institutional Review Board
IRC	independent review committee
KL-6	Krebs von den Lungen-6
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute (of the United States)
NE	not evaluable
NED	no evidence of disease
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression free survival
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PR	partial response
QD	once daily
QLQ	Quality of Life Questionnaire
QLQ-LC13	Quality of Life Questionnaire, lung cancer module
QOL	quality of life
QT	QT interval; a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QTc	heart rate-corrected QT interval (calculated)
QTcF	QT interval corrected (Fridericia)
Rac	accumulation ratio
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
SAE	serious adverse event
SD	stable disease

SP-D	surfactant protein-D
SRS	stereotactic radiosurgery
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
tmax	time of first occurrence of maximum observed concentration
tmax,ss	time of first occurrence of maximum observed concentration during a dosing interval, at steady state
UK	United Kingdom
US	United States
ULN	upper limit of normal
WBRT	whole brain radiation therapy
WHO	World Health Organization

4.0 OBJECTIVES

4.1 Primary Objectives

Phase 1 Part

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

Phase 2 Part

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

4.2 Secondary Objectives

Phase 1 Part

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

Phase 2 Part

1. To further characterize the efficacy of TAK-788 shown by confirmed ORR, as assessed by the investigator, duration of response, progression free survival (PFS), disease control rate (DCR), time to response by both investigator and IRC per RECIST v1.1 and overall survival (OS).
2. To assess the safety and tolerability of TAK-788.
3. To collect sparse plasma concentration-time data of TAK788 and its active metabolites, (including, but not limited to, AP32960 and AP32914), to contribute to population PK and exposure-response analyses.
4. To assess patient-reported symptoms (particular core symptoms of lung cancer), functioning, and health-related quality of life (HRQoL) with the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 and the EORTC lung cancer module QLQ-LC13.

4.3 Study Design

This is a Phase 1/2 study. Initially, the study started as a Phase 1 study to confirm the global RP2D of 160 mg QD in Japanese patients. After it was confirmed that the RP2D in Japanese

patients was the same as the global RP2D, a Phase 2 part was added; the Phase 2 part is designed to evaluate the efficacy and safety of TAK-788 in treatment naive Japanese NSCLC patients with EGFR exon 20 insertion mutation.

Phase 1 Part

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

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

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

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

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

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

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

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

Phase 2 Part

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

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

5.0 ANALYSIS ENDPOINTS

5.1.1 Phase 1 Part

5.1.1.1 Primary Endpoint

The primary endpoint is:

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

5.1.1.2 Secondary Endpoints

The secondary endpoints are:

1. Safety profile of orally administered TAK-788:
   - The number and percentage of patients with treatment-emergent adverse events (TEAEs).

- The number and percentage of patients with first cycle DLTs.

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

5.1.1.3 Safety Endpoints

The safety endpoints are:

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

5.1.2 Phase 2 Part

5.1.2.1 Primary Endpoint:

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

5.1.2.2 Secondary Endpoints:

1. Confirmed ORR, as assessed by the investigator, per RECIST v1.1.
2. Duration of response, as assessed by the IRC and the investigator.
3. Time to response, as assessed by the IRC and the investigator.
4. DCR (the percentage of patients with best response of complete response [CR], partial response [PR], or SD of 42 days or longer), as assessed by the IRC and the investigator, per RECIST v1.1.
5. PFS, as assessed by the IRC and the investigator.
6. OS.

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

5.1.2.3 Safety Endpoints:

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

6.0 DETERMINATION OF SAMPLE SIZE

Phase 1 Part

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

Phase 2 Part

The purpose of the Phase 2 part of this study is to determine the confirmed ORR of orally administered TAK-788 as the first line treatment at RP2D determined in the Phase 1 part in patients with NSCLC with EGFR exon 20 insertion mutations. The sample size was determined so that it would allow us to state that the true ORR is greater than threshold response rate of 35%. The expected true ORR of TAK-788 is 60% in treatment naive population. Twenty-six (26) patients with NSCLC with tumors harboring EGFR exon 20 insertion mutations with confirmation of central test will allow the study to have over 80% power to rule out an uninteresting rate of 35% in this population with a 1-sided alpha of 0.05 according to the two-stage design with futility and efficacy interim analysis described in Section 7.12.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

7.1.1 Study Definitions

The following definitions and calculation formulas will be used.

- Descriptive statistics: Number of subjects, mean, standard deviation, maximum, minimum, and quartiles.

- Subjects who were enrolled in the expansion cohort of the Phase 1 part will be analyzed as the dose level which they were initially dosed (i.e. 160 mg).
- BMI (kg/m^2): Weight (kg) / height $(m)^2$
- Conventions of the number of days to weeks, cycles, months, and years:
  - 1 cycle = 28 days
  - 1 week = 7 days
  - 1 month = 30.4375 days
  - 1 year = 365.25 days
- Duration of exposure to study drug (days): (Date of last study dose – date of the first dose of study drug + 1) if date of last study drug is non-missing; otherwise (Date of data cutoff – date of the first dose of study drug + 1).
- Duration of exposure to study drug (months): Duration of exposure to study drug (days) / 30.4375.
- Duration of follow-up (months) (Phase 2 part only): (Last alive date – date of the first dose of study drug + 1) / 30.4375.
  Last alive date is the latest non-missing date among Alive Date (Interim), Alive Date (26 Patients C7D1), and Alive Date (Final).
- Dose intensity (mg/day): Total amount of doses taken (mg) / duration of exposure to study drug (days).
- Relative dose intensity (%): Dose intensity (mg/day) / intended dose intensity (mg/day), where the intended dose intensity does not consider intra-patient dose escalation.
- Time since initial diagnosis (months): (Date of the first dose of study drug – date of initial diagnosis) / 30.4375.
  For incomplete initial diagnosis date, if day is missing but month and year are non-missing, impute as 1st of the month; if day and month are missing, impute as Jan 1st of the year.
- Non-squamous: Adenocarcinoma, Adenosquamous carcinoma, Large cell or Other.
- CNS involvement: Involvement of Brain – Leptomeningeal, Brain – Parenchymal, Leptomeningeal, Spinal Cord – Leptomeningeal, or Spinal Cord – Parenchymal.
- TEAE leading to study drug modification: Any TEAE leading to dose reduction, dose interruption or dose discontinuation.
- ILD/Pneumonitis: A narrow search strategy will be used for the retrieval of all PTs from Interstitial lung disease (SMQ). Further details are given in Appendix.

7.1.2 Definition of Efficacy Endpoints

Phase 1 part: ORR

ORR is defined as the proportion of the patients whose best overall response is CR or PR, per RECIST v1.1, after the initiation of study treatment as assessed by the investigator.

Phase 2 part: Confirmed ORR

Confirmed ORR is defined as the proportion of the patients whose best overall response is confirmed CR or confirmed PR, per RECIST v1.1, after the initiation of study treatment as assessed by IRC/investigator.

Phase 2 part: Best percent change in target lesion (%)

Best percent change in target lesion is defined as the best percent change from baseline in the sum of target lesion diameters.

Only the target lesion diameters measured by IRC on or prior to the earlier of the date of PFS event or date of censoring for PFS by IRC will be used in order to calculate the best percent change.

Phase 2 part: Duration of response

For patients with confirmed CR/PR per RESIST v1.1, DOR is defined as the time from the first observation of CR/PR (whichever is first recorded) to the first date at which progressive disease is objectively documented per RECIST v1.1 or death due to any cause, whichever occurs first. DOR will be expressed in month, i.e. DOR = (earliest date of progression or death – date of first CR/PR + 1) / 30.4375. The same censoring rules as those for PFS will be applied.

Phase 2 part: Time to response

For patients with confirmed CR/PR per RECIST v1.1, time to response is defined as the time from the date of the first dose of study treatment to the first observation of CR/PR (whichever is first recorded).

Phase 2 part: DCR

DCR is defined as the proportion of patients whose best overall response is confirmed CR, confirmed PR, or SD, per RECIST v1.1, as assessed by IRC/investigator.

Phase 2 part: PFS

PFS is defined as the time from the date of the first dose of study treatment to the first date at which disease progression is objectively documented per RECIST v1.1, or death due to any cause, whichever occurs first. PFS will be expressed in month, i.e. PFS = (earliest date of progression or death – date of the first dose + 1) / 30.4375.

Only adequate tumor assessments (overall response of CR, PR, SD, Non-CR/Non-PD or PD) will be considered in the determination of progression and censoring date. General censoring rules for PFS will be as follows:

- Subjects who have no tumor assessment performed at screening will be censored on Day 1.

- Subjects who have no adequate tumor assessment after the initiation of study treatment will be censored on Day 1, except that death occurred within 126 days after the initiation of study treatment will be a PFS event at death date unless the subjects receive subsequent anticancer therapy or subsequent surgery/procedure prior to death.
- Subjects who experience no documented disease progression or death will be censored on the date of last adequate tumor assessment.
- Subjects who experience disease progression or death >126 days of last adequate tumor assessment will be censored on the date of last adequate tumor assessment prior to the 126-day interval.
- Subjects who receive subsequent anticancer therapy prior to documented disease progression or death will be censored on the date of the last adequate tumor assessment on or prior to the date of initiation the subsequent treatment.
- Subjects who receive subsequent surgery/procedure prior to documented disease progression or death will be censored on the date of the last adequate tumor assessment on or prior to the date of the surgery/procedure.

Phase 2 part: OS

OS is defined as the time from the date of the first dose to death due to any cause. Subjects who are known to be alive will be censored on the last date when the subjects are known to be alive. OS will be expressed in month, i.e. OS = (date of death – date of the first dose + 1) / 30.4375.

7.1.3 Definition of Study Days

Study Day 1 is defined as the date on which a subject is administered their first dose of the study drug. Other study days are defined relative to the Study Day 1 with Day 1 being Study Day 1 and Day -1 being the day prior to Study Day 1.

7.1.4 Definition of Study Visit Windows

For each parameter, data obtained after the date of subsequent anticancer therapy or subsequent surgery/procedure (whichever is first recorded) will not be used. All evaluable data will be handled according to the following rules.

For each visit, observation obtained in the corresponding time interval will be used. If more than one observation lies within the same visit window, the observation with the closest Study Day to the scheduled Study Day will be used. If there are two observations equidistant to the scheduled Study Day, the later observation will be used.

Table 7.a Visit Window for Clinical Laboratory Evaluations, Vital Signs and Weight

Visit	Scheduled Study Day	Time Interval	
		Study Day	Follow-up Day
Cycle 1, Day 1	Study Day: 1	<= 1	
Cycle 1, Day 15	Study Day: 15	Scheduled Study Day ± 5	
Cycle 2, Day 1	Study Day: 29	Scheduled Study Day ± 7	<23
Cycle (n) (Cycle 3 and subsequent Cycles), Day 1	Study Day: 28 * (n - 1) + 1	Scheduled Study Day ± 7	<23
30 Days After Last Dose	Follow-up Day: 30		23 – 37

Table 7.b Visit Window for 12-lead ECGs

Visit	Scheduled Study Day	Time Interval	
		Study Day	Follow-up Day
Cycle 1, Day 1	Study Day: 1	<= 1	
Cycle 2, Day 1	Study Day: 29	Scheduled Study Day ± 7	<23
Cycle (n) (Cycle 3 and subsequent Cycles), Day 1	Study Day: 28 * (n - 1) + 1	Scheduled Study Day ± 7	<23
30 Days After Last Dose	Follow-up Day: 30		23 – 37

Table 7.c Visit Window for Patient Reported Outcome (Phase 2 part)

Visit	Scheduled Study Day	Time Interval	
		Study Day	Follow-up Day
Cycle 1, Day 1	Study Day: 1	<= 1	
Cycle 2, Day 1	Study Day: 29	Scheduled Study Day ± 7	<23
Cycle (n) (Cycle 3 – Cycle 14, Cycle 15 and every 12 weeks [3 Cycles] thereafter), Day 1	Study Day: 28 * (n - 1) + 1	Scheduled Study Day ± 7	<23
30 Days After Last Dose	Follow-up Day: 30		23 – 37

7.1.5 Conventions for Missing Adverse Event Dates

Not applicable.

7.1.6 Conventions for Missing Concomitant Medication Dates

Not applicable.

7.1.7 Handling of Dropouts or Missing Data

Missing test results will not be used for the analyses unless specified.

For best overall response by IRC, subjects who have no best overall response will be treated as NE.

For plasma concentrations and laboratory test results, values below the lower limit of quantification will be treated as zero when calculating the descriptive statistics. For laboratory test results, values above the upper limit of quantification will be treated as the upper limit value when calculating the descriptive statistics.

7.2 Analysis Sets

Phase 1 Part

- Safety population:

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

- Pharmacokinetic population:

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

- DLT-evaluable population:

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

- Response-evaluable population:

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

Phase 2 Part

- Safety population:

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

- Centrally confirmed population:

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

- FAS:

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

7.3 Disposition of Subjects

7.3.1 Study Information

Analysis Set:

All Subjects Who Signed the Informed Consent Form

Analysis Variable(s):

Date First Subject Signed Informed Consent Form

Date of Data Cutoff

MedDRA Version

WHO Drug Version

SAS Version Used for Creating the Datasets

Analytical Method(s):

(1) Study Information

Study information shown in the analysis variables section will be provided.

7.3.2 Screen Failures

Analysis Set:

All Subjects Who Did Not Enter the Treatment Period

Analysis Variables:

Age (years)

Gender [Male, Female]

Analytical Methods:

(1) Screen Failures

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided separately for patients in the Phase 1 part and the Phase 2 part.

7.3.3 Subject Eligibility

Analysis Set:

All Subjects Who Signed the Informed Consent Form

Analysis Variable(s):

Eligibility Status

[Eligible for Entrance into the Treatment Period, Not Eligible for Entrance into the Treatment Period]

Primary Reason for Subject Not Being Eligible

[Death, Adverse Event, Screen Failure, Protocol Deviation, Lost to Follow-up, Withdrawal by Subject, Study Terminated by Sponsor, Other]

Analytical Method(s):

(1) Eligibility for Entrance into the Treatment Period

Frequency distributions will be provided separately for patients in the Phase 1 part and the Phase 2 part. When calculating percentages for the primary reasons for subject not being eligible, the total number of ineligible subjects will be used as the denominator.

7.3.4 Number of Subjects Who Entered the Treatment Period by Site

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Variables:

Status of Entrance into the Treatment Period [Entered]

Stratum:

Site [Site numbers will be used as categories]

Analytical Methods:

(1) Number of Subjects Who Entered the Treatment Period by Site

Frequency distributions will be provided for each stratum by dose and overall for the Phase 1 part, and overall for the Phase 2 part.

7.3.5 Disposition of Subjects

Analysis Set:

All Subjects Who Were Enrolled

Analysis Variables:

Study Drug Administration Status

[Eligible but Not Treated]

Reason for Not Being Treated

[Adverse Event, Protocol Deviation, Progressive Disease, Symptomatic Deterioration, Unsatisfactory Therapeutic Response, Pregnancy, Study Terminated by Sponsor, Withdrawal by Subject, Lost to Follow-up, Other]

Study Drug Completion Status

[Ongoing, Completed (Phase 1 part only), Discontinued Study Drug]

Reason for Discontinuation of Study Drug

[Adverse Event, Protocol Deviation, Progressive Disease, Symptomatic Deterioration, Unsatisfactory Therapeutic Response, Pregnancy, Study Terminated by Sponsor, Withdrawal by Subject, Lost to Follow-up, Other]

Completion Status of Follow-up (Phase 1 part) / 30 Days after Last Dose (Phase 2 part)

[Ongoing, Completed, Discontinued]

Reason for Discontinuation

[Lost to Follow-up, Study Terminated by Sponsor, Withdrawal by Subject, Death, Other]

Analytical Methods:

(1) Disposition of Subjects.

Frequency distributions will be provided by dose and overall for the Phase 1 part, and overall for the Phase 2 part. When calculating percentages for the reasons for not being treated, the total number of subjects not treated by the study drug will be used as the denominator. When calculating percentages for the reasons for discontinuation, the total number of subjects who prematurely discontinued will be used as the denominator

7.3.6 Protocol Deviations Protocol Deviations and Analysis Sets

7.3.6.1 Protocol Deviations

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Variable(s):

Significant Protocol Deviation

[Entry Criteria, Concomitant Medication, Procedure Not Performed Per Protocol, Study Medication, Withdrawal Criteria, Major GCP Violations]

Analytical Method(s):

(1) Protocol Deviations

For each deviation category, frequency distribution will be provided by dose and overall for the Phase 1 part, and overall for the Phase 2 part. A subject who has several deviations will be counted once in each appropriate category. A subject who has several deviations that can be classified into the same category will be counted only once.

7.3.6.2 Analysis Sets

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Variable(s):

Handling of Subjects

[Categories are based on the specifications in Subject Evaluability List]

Analysis Sets

Safety population	[Included]
Pharmacokinetic population (Phase 1 part only)	[Included]
DLT-evaluable population (Phase 1 part only)	[Included]
Response-evaluable population (Phase 1 part only)	[Included]
Centrally confirmed population (Phase 2 part only)	[Included]
Full Analysis Set (Phase 2 part only)	[Included]

Analytical Method(s):

(1) Subjects Excluded from Analysis Sets

(2) Analysis Sets

Frequency distributions will be provided. For Phase 1 part, it will be provided by dose for (1), and by dose and overall for (2). For (1), a subject who has several reasons for exclusion will be counted once in each appropriate category. A subject who has several reasons for exclusion that can be classified into the same category will be counted only once.

7.4 Demographic and Other Baseline Characteristics

Analysis Set:

Safety population

Centrally confirmed population (Phase 2 part only)

Analysis Variables:

Age (years) [Min<= - <65, 65<= - <=Max]

[Min<= - <50, 50<= - <65, 65<= - <75, 75<= - <=Max]

Gender [Male, Female]

Height (cm)

Weight (kg) at Baseline

BMI (kg/m2) at Baseline

Smoking History

[Never, Current, Former]

ECOG Performance Status at Baseline

[0, 1, 2, 3, 4]

Stage at Initial Diagnosis

[IA, IB, IIA, IIB, IIIA, IIIB, IIIC, IV, Unknown or not staged] (Phase 1 part)

[IA, IB, IIA, IIB, IIIA, IIIB, IIIC, IVA, IVB, Unknown or not staged] (Phase 2 part)

Stage at Screening

[IIIB, IIIC, IV, Refractory, Other] (Phase 1 part)

[IIIA, IIIB, IIIC, IVA, IVB, Other] (Phase 2 part)

Time since Initial Diagnosis (months)

Histopathological Classification of NSCLC

[Adenocarcinoma, Adenosquamous carcinoma, Large cell, Squamous, Unknown, Other]

[Non-squamous, Squamous, Unknown]

Lung Involvement at Screening

[Left, Right, Both, Not involved]

Number of Organ Involvement at Screening

[0, 1, 2, 3<= - <=Max]

CNS Involvement at Screening

[Yes, No]

Number of Prior Anticancer Regimens

[0, 1, 2, 3<= - <=Max]

EGFR Genetic Status in Tumor Tissue Assessed (Phase 1 part only)

[Yes, No]

EGFR Mutation Method of assessment (Phase 1 part only)

[Sequencing, PCR, Other]

EGFR Abnormality Detected (Phase 1 part only)

[Yes, No]

EGFR Exon 20 Insertion Mutation Detected by Local Test

[Yes, No]

EGFR Exon 20 Insertion Mutation Confirmed by Central Test (Phase 2 part only)

[Yes, No]

EGFR Exon 20 Insertion Mutation Type (Phase 1 part)

A763_Y764insFQEA	[Yes]
V769_D770insASV	[Yes]
D770_N771insNPG	[Yes]
D770_N771insSVD	[Yes]
H773_V774insNPH	[Yes]
Other	[Yes]

Other EGFR Mutation Detected (Phase 1 part only)

[Yes, No]

Other EGFR Mutation Type (Phase 1 part only)

Exon 19 Deletion	[Yes]
G719A	[Yes]
G719C	[Yes]
G719S	[Yes]
S768I	[Yes]
T790M	[Yes]
L858R	[Yes]
L861Q	[Yes]
L861R	[Yes]
Other	[Yes]

HER2 Genetic Status in Tumor Tissue Assessed

[Yes, No]

HER2 Mutation Method of assessment

[Sequencing, PCR, Other]

HER2 Abnormality Detected [Yes, No]

HER2 Exon 20 Insertion Mutation Detected by Local Test [Yes, No]

HER2 Exon 20 Insertion Mutation Type

M774_A775insAYVM [Yes]

A775_G776insYVMA [Yes]

G776_V777insVC [Yes]

P780_Y781insGSP [Yes]

Other [Yes]

Other HER2 Mutation Detected [Yes, No]

Other HER2 Mutation Type

L755S [Yes]

G776V [Yes]

V777L [Yes]

Other [Yes]

Analytical Methods:

(1) Summary of Demographics and Baseline Characteristics

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided by dose and overall for the Phase 1 part, and overall for the Phase 2 part.

7.5 Medical History and Concurrent Medical Conditions

Analysis Set:

Safety population

Analysis Variables:

Medical History

Concurrent Medical Conditions

Analytical Methods:

(1) Medical History by System Organ Class and Preferred Term

(2) Concurrent Medical Conditions by System Organ Class and Preferred Term

Frequency distributions will be provided by dose and overall for the Phase 1 part, and overall for the Phase 2 part. MedDRA dictionary will be used for coding. Summaries will

be provided using SOC and PT, where SOC will be sorted alphabetically and PT will be sorted in decreasing frequency.

A subject with multiple occurrences of medical history or concurrent medical condition within a SOC will be counted only once in that SOC. A subject with multiple occurrences of medical history or concurrent medical condition within a PT will be counted only once in that PT.

7.6 Medication History and Concomitant Medications

Analysis Set:

Safety population

Analysis Variables:

Prior Anticancer Therapy

Concomitant Medications

Analytical Methods:

(1) Prior Anticancer Therapy by Preferred Medication Name.

(2) Concomitant Medications That Started and Stopped Prior to Baseline by Preferred Medication Name.

(3) Concomitant Medications That Started Prior to and Were Ongoing at Baseline as well as Those That Started After Baseline by Preferred Medication Name.

Frequency distributions will be provided by dose and overall for the Phase 1 part, and overall for the Phase 2 part. WHO Drug dictionary will be used for coding. Summaries will be provided using preferred medication names and sorted in decreasing frequency based on the number of reports. A subject who has been administered several medications with the same preferred medication name will be counted only once for that preferred medication name.

7.7 Study Drug Exposure and Compliance

Analysis Set:

Safety population

Analysis Variable(s):

Duration of Exposure to Study Drug (days)

Duration of Exposure to Study Drug (months)

[Min<= - <1, 1<= - <3, 3<= - <6, 6<= - <12, 12<= - <=Max]

Duration of Follow-up (months) (Phase 2 part only)

Total Amount of Doses Taken (mg)

Dose Intensity (mg/day)

Relative Dose Intensity (%)

Analytical Method(s):

(1) Study Drug Exposure and Compliance

Frequency distributions and descriptive statistics for continuous variables will be provided by dose and overall for the Phase 1 part, and overall for the Phase 2 part.

7.8 Efficacy Analysis

7.8.1 Primary Efficacy Endpoint(s) (Phase 2 part only)

7.8.1.1 *Primary Analysis*

Analysis Set:

Centrally confirmed population for IA

Analysis Variables:

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

Analytical Methods:

The interim analysis was performed based on the centrally confirmed population for IA, which consists of the first 14 patients who have confirmed harboring EGFR exon 20 insertion mutation by central test and have received at least 1 dose of TAK-788. As the number of patients with confirmed objective response, per IRC, was 5 or fewer in the 14 "centrally confirmed" patients, enrollment was stopped entirely for futility, and the IA will be the primary analysis for the Phase 2 part.

For details on the interim analysis plan for the Phase 2 part, refer to Section 7.12.

Best overall response by IRC will be summarized using the categories of CR, PR, SD, Non-CR/Non-PD, PD, NED and NE. The point estimate and 2-sided 90% exact CI will be provided. For this analysis, the best overall response at the interim analysis will be used without any update.

7.8.1.2 *Secondary Analysis*

Analysis Set:

Centrally confirmed population

FAS

Analysis Variables:

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

Analytical Methods:

Best overall response by IRC will be summarized using the categories of CR, PR, SD, Non-CR/Non-PD, PD, NED and NE. For this analysis, the best overall response at the data cutoff will be used. The data cutoff may occur multiple times.

Confirmed ORR, as assessed by IRC, and the 2-sided 95% exact CI will be provided.

7.8.2 Secondary Efficacy Endpoint(s) (Phase 1 Part)

Analysis Set:

Response-evaluable population

Analysis Variables:

Investigator assessed ORR using RECIST v1.1

Subgroups:

EGFR Exon 20 Insertion Mutation Detected	[Yes]
Other EGFR Mutation Detected	[Yes]
HER2 Exon 20 Insertion Mutation Detected	[Yes]
Other HER2 Mutation Detected	[Yes]
EGFR or HER2 Abnormality Detected	[No]

Analytical Methods:

Best overall response by investigator will be summarized using the categories of CR, PR, SD, PD and NE.

Investigator assessed ORR and the 2-sided 95% exact CI will be provided by dose for overall and for the above each subgroup.

7.8.3 Secondary Efficacy Endpoint(s) (Phase 2 Part)

Analysis Set:

Centrally confirmed population

FAS

Analysis Variables:

Confirmed ORR, as assessed by investigator, per RECIST v1.1

Best percent change in target lesion, as assessed by IRC

Duration of response, as assessed by IRC

Duration of response, as assessed by investigator

Time to response, as assessed by IRC

Time to response, as assessed by investigator

DCR, as assessed by IRC, per RECIST v1.1

DCR, as assessed by investigator, per RECIST v1.1

PFS, as assessed by IRC

PFS, as assessed by investigator

OS

Analytical Methods:

(1) Confirmed ORR, as assessed by investigator, per RECIST 1.1

Best overall response by investigator will be summarized using the categories of CR, PR, SD, PD and NE.

Confirmed ORR, as assessed by investigator, and the 2-sided 95% exact CI will be provided.

(2) Best percent change in target lesion, as assessed by IRC

For best percent change in target lesion, as assessed by IRC, a waterfall plot will be presented.

(3) Duration of response

Duration of response, as assessed by IRC, will be analyzed using the Kaplan-Meier method. The median as well as proportion remaining in response at 6, 12, 18, and 24 months will be provided along with 95% CIs.

Similar analysis will also be conducted for duration of response, as assessed by investigator.

(4) Time to response

Time to response, as assessed by IRC, will be summarized using the descriptive statistics. The analysis of time to response will only include patients with confirmed CR or confirmed PR.

Similar analysis will also be conducted for time to response, as assessed by investigator.

(5) DCR

DCR, as assessed by IRC, and the 2-sided 95% exact CI will be provided.

Similar analysis will also be conducted for DCR, as assessed by investigator.

(6) PFS

PFS, as assessed by IRC, will be analyzed using the Kaplan-Meier method. Median PFS as well as rates at 6, 12, 18, and 24 months will be provided along with 95% CIs.

Similar analysis will also be conducted for PFS, as assessed by investigator.

(7) OS

OS will be analyzed using the Kaplan-Meier method. Median OS as well as rates at 6, 12, 18, and 24 months will be provided along with 95% CIs.

7.8.4 Additional Efficacy Endpoint(s) (Phase 2 Part)

7.8.4.1 Subgroup analyses

Analysis Set:

Centrally confirmed population

FAS

Analysis Variables:

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

Subgroups:

Age (years)	[Min<= - <65, 65<= - <=Max]
Gender	[Male, Female]
CNS Involvement at Screening	[Yes, No]
EGFR Exon 20 Insertion Mutation Confirmed by Central Test	[Yes, No]

Analytical Methods:

Confirmed ORR, as assessed by IRC, and the 2-sided 95% exact CI will be provided for the above each subgroup.

7.8.4.2 Overall response by patient

Analysis Set:

FAS

Analysis Variables:

Overall response, as assessed by IRC, per RECIST v1.1

Analytical Methods:

A swim-lane plot of overall response, as assessed by IRC, by patient will be provided. Centrally confirmed population and the rest of the FAS will be separately presented.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

The plasma concentration-time data of TAK-788 and its active metabolites, including, but not limited to, AP32960 and AP32914 from the Phase 2 part will be pooled with data from other TAK-788 clinical studies in patients with cancer to contribute to population PK analyses. Results of the population PK analyses of data from this study will also contribute to exposure-response

analyses of safety and efficacy. The analysis plans for the population PK and exposure-response analyses will be separately defined, and the results of these analyses will be reported separately.

7.9.1 Pharmacokinetic Analysis (Phase 1 part only)

7.9.1.1 *Plasma Concentrations*

Analysis Set:

Pharmacokinetic population

Analysis Variable(s):

Plasma Concentrations of TAK-788, AP32960 and AP32914

Visit:

Cycle 1 Day 1 and Cycle 2 Day 1: Predose, 0.5, 1, 2, 4, 6, 8, 24* hours postdose

* 24 hours postdose at Cycle 1 Day 1 correspond to Cycle 1 Day 2 predose.
24 hours postdose at Cycle 2 Day 1 correspond to Cycle 2 Day 2 predose.

Analytical Method(s):

The following summaries will be provided by dose.

(1) Summary of Plasma Concentrations by Visit

Descriptive statistics and CV will be provided by visit.

(2) Mean and Standard Deviation Plot of Plasma Concentrations on Cycle 1 Day 1 and Cycle 2 Day 1

Mean and standard deviation will be plotted. Relative nominal time since last dose (numerical) will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis for Cycle 1 Day 1 and Cycle 2 Day 1, separately. The vertical axis will be a normal scale.

(3) Mean Plot of Plasma Concentrations on Cycle 1 Day 1 and Cycle 2 Day 1

Mean will be plotted. Relative nominal time since last dose (numerical) will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis for Cycle 1 Day 1 and Cycle 2 Day 1, separately. The vertical axis will be a common logarithmic scale.

(4) Plot of Individual Plasma Concentrations on Cycle 1 Day 1 and Cycle 2 Day 1

Individual plasma concentrations will be plotted. Relative actual time since last dose (numerical) will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis for Cycle 1 Day 1 and Cycle 2 Day 1, separately. The vertical axis will be a normal scale.

(5) Plot of Individual Plasma Concentrations on Cycle 1 Day 1 and Cycle 2 Day 1

Individual plasma concentrations will be plotted. Relative actual time since last dose (numerical) will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis for Cycle 1 Day 1 and Cycle 2 Day 1, separately. The vertical axis will be a common logarithmic scale.

7.9.1.2 Pharmacokinetic Parameters

Analysis Set:

Pharmacokinetic population

Analysis Variable(s):

Pharmacokinetic parameters of TAK-788, AP32960 and AP32914

tmax, tmax,ss, Cmax, Cmax,ss, AUClast, AUClast,ss, AUC24, AUC24,ss,
dn-Cmax, dn-Cmax,ss, dn-AUClast, dn-AUClast,ss, dn-AUC24, dn-AUC24,ss,
Cav, Cav,ss, t1/2zeff, Rac(Cmax), Rac(AUC24), Molar Cmax, Molar Cmax,ss,
Molar AUClast, Molar AUClast,ss, Molar AUC24, Molar AUC24,ss,
Molar Cav, Molar Cav,ss

Combined pharmacokinetic parameters

Combined Molar Cmax, Combined Molar Cmax,ss,
Combined Molar AUC24, Combined Molar AUC24,ss,
Combined Molar Cav, Combined Molar Cav,ss,
Rac(Combined Molar AUC24), Rac(Combined Molar Cmax)

Pharmacokinetic parameters of AP32960 and AP32914

Molar AUC24 Ratio, Molar AUC24,ss Ratio

Analytical Method(s):

The following summaries will be provided by dose.

(1) Summary of Pharmacokinetic Parameters

Descriptive statistics, CV, geometric mean, and geometric CV will be provided.

7.9.1.3 Assessment of Dose Proportionality in Pharmacokinetic Parameters

Analysis Set:

Pharmacokinetic population

Analysis Variable(s):

Pharmacokinetic parameters of TAK-788

Cmax, Cmax,ss, AUC24, AUC24,ss

Combined pharmacokinetic parameters

Combined Molar Cmax, Combined Molar Cmax,ss,

Combined Molar AUC24, Combined Molar AUC24,ss,

Analytical Method(s):

The following summaries will be provided.

(1) Regression Analysis of Pharmacokinetic Parameters on Dose

A power regression analysis will be performed for each analysis variable using the power model:

$$y = a * (dose)^b * e,$$

where y is the analysis variable, a and b are the regression parameters, and e is the error term of the power equation.

A linear regression will also be performed using the linear model:

$$y = a + b*(dose) + e.$$

Parameter estimates for a and b, and their 2-sided 90% confidence intervals will be provided for each model. Dose proportionality will be declared if the 90% confidence interval of the slope (i.e. b) based on a power regression model lies entirely within the critical region defined by $1 + \ln(L)/\ln(r)$ to $1 + \ln(U)/\ln(r)$, where r is the ratio of the highest and lowest dose in the dose range and (L,U) = (0.5, 2) for the Hummel Critical Region.

7.9.2 Pharmacodynamic Analysis

Not applicable.

7.10 Other Outcomes

7.10.1 Patient-Reported Outcome (Phase 2 Part)

Analysis Set:

FAS

Analysis Variables:

EORTC QLQ-C30

Global health status

Global health status

Function Scales

Physical functioning

Role functioning

Emotional functioning

Cognitive functioning

Social functioning

Symptom Scales

Fatigue

Nausea and vomiting

Pain

Dyspnoea

Insomnia

Appetite loss

Constipation

Diarrhoea

Financial difficulties

EORTC QLQ-LC13

Dyspnoea

Coughing

Haemoptysis

Sore mouth

Dysphagia

Peripheral neuropathy

Alopecia

Pain in chest

Pain in arm or shoulder

Pain in other parts

Visit:

Baseline, Cycle 2, Cycle 3, Cycle 4, Cycle 5, Cycle 6, Cycle 7, Cycle 8, Cycle 9, Cycle 10, Cycle 11, Cycle 12, Cycle 13, Cycle 14, Cycle 15, Cycle 18, Every 12 Weeks (3 Cycles) thereafter

Analytical Methods:

The QLQ-C30 and QLQ-LC13 subscale scores will be derived according to the EORTC QLQ-C30 (v3.0) Scoring Manual and summarized as follows.

(1) Summary of EORTC QLQ-C30 subscale scores

Descriptive statistics for observed values and changes from baseline will be provided for each visit.

Mean will be plotted for each visit with standard deviation bars.

(2) Summary of EORTC QLQ-LC13 subscale scores

Descriptive statistics for observed values and changes from baseline will be provided for each visit.

Mean will be plotted for each visit with standard deviation bars.

7.11 Safety Analysis

7.11.1 Adverse Events

7.11.1.1 Overview of Treatment-Emergent Adverse Events

Analysis Set:

Safety population

Analysis Variable(s):

TEAE

Categories:

Relationship to Study Drug [Related, Not Related]

Analytical Method(s):

The following summaries will be provided by dose separately for patients in the Phase 1 part and the Phase 2 part.

(1) Overview of Treatment-Emergent Adverse Events

1. All Treatment-Emergent Adverse Events (number of events, number and percentage of subjects).
2. Relationship of Treatment-Emergent Adverse Events to study drug (number of events, number and percentage of subjects).
3. Grade 3 or higher Treatment-Emergent Adverse Events (number of events, number and percentage of subjects).
4. Grade 3 or higher Drug-Related Treatment-Emergent Adverse Events (number of events, number and percentage of subjects).

5. Treatment-Emergent Adverse Events leading to study drug dose modification (number of events, number and percentage of subjects).
6. Treatment-Emergent Adverse Events leading to study drug discontinuation (number of events, number and percentage of subjects).
7. Treatment-Emergent Adverse Events leading to study drug reduction (number of events, number and percentage of subjects).
8. Treatment-Emergent Adverse Events leading to study drug interruption (number of events, number and percentage of subjects).
9. Serious Treatment-Emergent Adverse Events (number of events, number and percentage of subjects).
10. Relationship of serious Treatment-Emergent Adverse Events to study drug (number of events, number and percentage of subjects).
11. Serious Treatment-Emergent Adverse Events leading to study drug discontinuation (number of events, number and percentage of subjects).
12. Treatment-Emergent Adverse Events resulting in death (number of events, number and percentage of subjects).
13. Drug-Related Treatment-Emergent Adverse Events resulting in death (number of events, number and percentage of subjects).

TEAEs will be counted according to the rules below. Percentages will be based on the number of subjects in the safety population.

Number of subjects

- Summaries for 2) and 10)

  A subject with occurrences of TEAE in both categories (ie, Related and Not Related) will be counted once in the Related category.

- Summaries other than 2) and 10)

  A subject with multiple occurrences of TEAE will be counted only once.

  Number of events

  For each summary, the total number of events will be calculated.

7.11.1.2 *Frequency of Subjects with DLTs during Cycle 1 (Phase 1 part only)*

Analysis Set:

DLT-evaluable population.

Analysis Variable(s):

DLTs during Cycle 1.

Analytical Method(s):

The number and percentage of Subjects with DLTs will be provided by dose.

7.11.1.3 Displays of Treatment-Emergent Adverse events

Analysis Set:

Safety population

Analysis Variable(s):

TEAE

Analytical Method(s):

The following summaries will be provided using frequency distribution by dose separately for patients in the Phase 1 part and the Phase 2 part.

TEAEs will be coded using the MedDRA (version 23.0 or higher) and will be summarized using SOC and PT.

SOC will be sorted alphabetically and PT will be sorted in decreasing frequency for tables provided by SOC and PT. SOC and PT will be sorted in decreasing frequency for tables provided by System Organ Class only or PT only.

(1) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.

(2) Treatment-Emergent Adverse Events by System Organ Class.

(3) Treatment-Emergent Adverse Events by Preferred Term.

(4) Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.

(5) Drug-Related Treatment-Emergent Adverse Events by Preferred Term.

(6) Grade 3 or higher Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.

(7) Grade 3 or higher Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.

(8) Toxicity Grade of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.

(9) Toxicity Grade of Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.

(10) Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.

(11) Serious and Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.

(12) Treatment-Emergent Adverse Events Leading to study drug dose modification by System Organ Class and Preferred Term

(13) Drug-Related Treatment-Emergent Adverse Events Leading to study drug dose modification by System Organ Class and Preferred Term

(14) Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term.

(15) Drug-Related Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term.

(16) Treatment-Emergent Adverse Events Leading to Study Drug Dose Reduction by System Organ Class and Preferred Term.

(17) Drug-Related Treatment-Emergent Adverse Events Leading to Study Drug Dose Reduction by System Organ Class and Preferred Term.

(18) Treatment-Emergent Adverse Events Leading to Study Drug Interruption by System Organ Class and Preferred Term.

(19) Drug-Related Treatment-Emergent Adverse Events Leading to Study Drug Interruption by System Organ Class and Preferred Term.

(20) Treatment-Emergent Adverse Events Resulting in Death by System Organ Class and Preferred Term.

(21) ILD/Pneumonitis Treatment-Emergent Adverse Events by Preferred Term (Any grade and Grade ≥3)

(22) Cardiac disorders Treatment-Emergent Adverse Events by Preferred Term (Any grade and Grade ≥3)

(23) Most Frequent Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Any grade and Grade ≥3)

(24) Most Frequent Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Any grade and Grade ≥3)

(25) Most Frequent Non-Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

The frequency distribution will be provided according to the rules below. Percentages will be based on the number of subjects in the safety population.

Number of subjects

- Summary tables other than (8) and (9).

  A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT.

- Summary tables for (8) and (9)

  A subject with multiple occurrences of TEAE within a SOC or a PT will be counted once for the TEAE with the maximum toxicity grade.

- Summary tables for (23) and (24).

  Most frequent TEAEs refer to PTs whose percentages are at least 10.0% in any one of the dose cohorts.

- Summary tables for (25).

  Most frequent Non-Serious TEAEs refer to PTs whose percentages are at least 5.0% in any one of the dose cohorts. If no Non-Serious TEAEs exceed a frequency of 5.0%, the frequency cut-off of 2.0% will be used.

7.11.1.4 Time to Initial Onset of Adverse Events of Clinical Interest

Analysis Set:

Safety population

Analysis Variable(s):

Time to Initial Onset of ILD/Pneumonitis

Time to Initial Onset of Diarrhoea

Time to Initial Onset of Cardiac disorders

Analytical Method(s):

(1) Time to Initial Onset of Adverse Events of Clinical Interest

Descriptive statistics of the time from the first day of study drug administration to first occurrence will be provided for each event for subjects experienced the corresponding event in the safety population for the Phase 1 part and Phase 2 part, separately.

7.11.1.5 Displays of Pretreatment Events

Analysis Set:

All Subjects Who Signed the Informed Consent Form

Analysis Variable(s):

PTE

Analytical Method(s):

The following summaries will be provided using frequency distribution separately for patients in the Phase 1 part and the Phase 2 part.

PTEs will be coded using the MedDRA and will be summarized using SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency.

(1) Pretreatment Events by System Organ Class and Preferred Term.

(2) Serious Pretreatment Events by System Organ Class and Preferred Term.

The frequency distribution will be provided according to the rules below.

Number of subjects

A subject with multiple occurrences of PTE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of PTE within a PT will be counted only once in that PT.

7.11.2 Clinical Laboratory Evaluations

7.11.2.1 Hematology and Serum Chemistry

Analysis Set:

Safety population

Analysis Variables:

Hematology

Hematocrit, Hemoglobin, Leukocytes with differential (Absolute neutrophil count, Basophils count, Eosinophils count, Lymphocytes count, Monocytes count), Platelets count

Serum Chemistry

Albumin, ALP, ALT, Amylase, AST, Bicarbonate, Total bilirubin, Direct bilirubin, Indirect bilirubin, BUN, Calcium, Chloride, Creatinine, CRP, Glucose, Lipase, Magnesium, Phosphate, Protein (total protein), Potassium, Sodium

Categories:

Toxicity Grade [Grade 0, Grade 1, Grade 2, Grade 3, Grade 4] (for summary (3))

[Grade 0 – Grade 2, Grade 3 – Grade 4] (for summary (4))

Visit:

Cycle 1: Baseline, Day 15

Cycle 2 and Thereafter: Day1

Analytical Methods:

For each variable, summaries (1) and (2) will be provided by dose separately for patients in the Phase 1 part and the Phase 2 part.

For appropriate variable, summary (3) and (4) will be provided by dose separately for patients in the Phase 1 part and the Phase 2 part. Data obtained after the date of subsequent anticancer therapy or subsequent surgery/procedure (whichever is first recorded) will not be used.

(1) Summary of Laboratory Test Results and Change from Baseline by Visit

Descriptive statistics for observed values and changes from baseline (each postdose visit - Baseline) will be provided for each visit.

(2) Case Plots of Laboratory Test Results

Plots over time for each subject will be presented.

(3) Summary of Shifts of Laboratory Test Results

Shift tables showing the number of subjects in each category of baseline grade and post-baseline maximum grade as defined by CTCAE will be provided.

(4) Number and Percentage of Subjects with Clinically Significant Abnormal Laboratory Values

Frequency distributions of post-baseline maximum grade for laboratory abnormalities will be provided. Subjects with baseline Grade ≥3 will be excluded from this analysis.

7.11.2.2 Urinalysis

Analysis Set:

Safety population

Analysis Variables:

pH

Specific gravity

Glucose [-, +-, 1+, 2+, 3+, 4+, 5+]

Ketones [-, +-, 1+, 2+, 3+, 4+, 5+]

Occult blood [-, +-, 1+, 2+, 3+, 4+, 5+]

Protein [-, +-, 1+, 2+, 3+, 4+, 5+]

Urobilinogen [-, +-, 1+, 2+, 3+, 4+, 5+]

Categories:

Toxicity Grade [Grade 0, Grade 1, Grade 2, Grade 3, Grade 4] (for summary (4))

[Grade 0 – Grade 2, Grade 3 – Grade 4] (for summary (5))

Visit:

Cycle 1: Baseline, Day 15

Cycle 2 and Thereafter: Day1

Analytical Methods:

For pH and specific gravity, summaries (1) and (2) will be provided by dose separately for patients in the Phase 1 part and the Phase 2 part.

For each variable other than pH and specific gravity, summary (3) will be provided by dose separately for patients in the Phase 1 part and the Phase 2 part.

For applicable variables, summary (4) and (5) will be provided by dose separately for patients in the Phase 1 part and the Phase 2 part. Data obtained after the date of subsequent anticancer therapy or subsequent surgery/procedure (whichever is first recorded) will not be used.

(1) Summary of Urine Laboratory Test Results and Change from Baseline by Visit

Descriptive statistics for observed values and changes from baseline (each postdose visit - Baseline) will be provided for each visit.

(2) Case Plots of Urine Laboratory Test Results

Plots over time for each subject will be presented.

(3) Number of Subjects in Categories of Urine Laboratory Test Results

Shift tables showing the number of subjects in each category at baseline and each postdose visit will be provided.

(4) Summary of Shifts of Laboratory Test Results

Shift tables showing the number of subjects in each category of baseline grade and post-baseline maximum grade as defined by CTCAE will be provided.

(5) Number and Percentage of Subjects with Clinically Significant Abnormal Urine Laboratory Values

Frequency distributions of post-baseline maximum grade for laboratory abnormalities will be provided. Subjects with baseline Grade ≥3 will be excluded from this analysis.

7.11.3 Vital Signs and Weight

Analysis Set:

Safety population

Analysis Variables:

Systolic Blood Pressure

Diastolic Blood Pressure

Pulse Rate

Respiratory Rate

Temperature

SpO2

Weight

Visit:

Cycle 1: Baseline, Day 15

Cycle 2 and Thereafter: Day 1

Analytical Methods:

For each variable, summaries (1) and (2) will be provided by dose separately for patients in the Phase 1 part and the Phase 2 part.

Summary of Vital Signs Parameters and Change from Baseline by Visit:

(1) Descriptive statistics for observed values and changes from baseline (each postdose visit - Baseline) will be provided for each visit.

(2) Case Plots.

Plots over time for each subject will be presented.

7.11.4 12-Lead ECGs

Analysis Set:

Safety population

Analysis Variables:

Interpretation

[Normal, Abnormal but not Clinically Significant, Abnormal and Clinically Significant]

QTcF Interval

Visit:

Cycle 1: Baseline

Cycle 2 and Thereafter: Day 1

Analytical Methods:

For QTcF interval, summaries (1) to (3) will be provided.

For 12-lead ECG interpretation, summary (4) will be provided.

(1) Summary of ECG Parameters and Change from Baseline by Visit

Descriptive statistics for observed values for each visit and changes from baseline will be provided

(2) Case Plots

Plots over time for each subject will be presented.

(3) Number and Percentage of Subjects with Clinically Significant Abnormal QTcF Measurements

Frequency distributions of post-baseline clinically significant abnormal QTcF measurements will be provided. Further details are given in Appendix.

(4) Summary of Shift of 12-lead ECG Interpretation

Shift table showing the number of subjects in each category for baseline result and the worst post-baseline result will be provided.

7.11.5 Other Observations Related to Safety

7.11.5.1 ECOG Performance Status

Analysis Set:

Safety population

Analysis Variables:

ECOG Performance Status

Analytical Methods:

(1) Summary of Shift of ECOG Performance Status

Shift table showing the number of subjects in each category for baseline result and the worst post-baseline result will be provided.

7.12 Interim Analysis

Phase 1 part: Not applicable.

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

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

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

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

7.12.1 Interim Efficacy Analysis

The interim analysis in the Phase 2 part will be performed based on the centrally confirmed population. Centrally confirmed population for IA consists of the first 14 patients who have confirmed harboring EGFR exon 20 insertion mutation by central test and have received at least 1 dose of TAK-788.

The primary efficacy endpoint for IA is Confirmed ORR, as assessed by the IRC, per RECIST v1.1.

Best overall response, as assessed by the IRC will be summarized using the categories of CR, PR, SD, Non-CR/Non-PD, PD, NED and NE. ORR, as assessed by the IRC, and the 2-sided 90% exact CI will be provided.

If it is concluded that TAK-788 is efficacious at IA (i.e. the number of patients with confirmed objective response is 9 or more in the 14 centrally confirmed patients), patients enrolled after the 14th patient will not be included in the FAS for the Phase 2 part.

7.13 Changes in the Statistical Analysis Plan

7.13.1 Changes from the protocol

The analyses described in the statistical analysis plan do not differ from those specified in the protocol.

7.13.2 Changes from the first version

An update (Version 2) was made to this plan on Apr 08, 2021 in which substantive changes were made.

- Protocol version on which the SAP is based was updated.
- Waterfall plot and swim-lane plot were added to further investigate the efficacy of TAK-788 in a visual way.
- EGFR Exon 20 Insertion Mutation Type was omitted after reviewing the priority of the analyses for the phase 2 part.
- Handling of missing best overall response by IRC was added.
- EORTC QLQ-C30 (v3.0) Scoring Manual was added to the reference list.
- FAS for the phase 2 part after confirming the efficacy of TAK-788 at IA was updated for clarity.

An update (Version 3) was made to this plan on Jan 14, 2022 in which substantive changes were made.

- Censoring rule for the subjects who died with no tumor assessment after the initiation of study treatment was clarified.
- Clarified that enrollment was stopped for futilty based on the IA results and thus IA will be the primary anaysis for the Phase 2 part.
- Secondary analysis of the primary endpoint for Centrally confirmed population was added.
- Clarified that swim-lane plot will be created for Centrally confirmed population and for the rest of the FAS separately.
- Summaries for Cardiac disorders (as adverse events of clinical interest) were added.

8.0 REFERENCES

[1] Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual (3rd Edition). Published by: European Organisation for Research and Treatment of Cancer, Brussels 2001.

[2] Jennison C, Turnbull BW. Group sequential methods with applications to clinical trials. Boca Raton, Florida:Chapman-Hall/CRC, 2000.

[3] Koyama T, Chen H. Proper inference from Simon's two-stage designs. Stat Med. 2008;27:3145–154.

[4] Mander AP, Thompson SG. Two-stage designs optimal under the alternative hypothesis for phase II cancer clinical trials. Contemporary Clinical Trials. 2010;31:572-8.

9.0 APPENDIX

9.1 Criteria for Clinically Significant Abnormal Values

For each parameter, data obtained after the date of subsequent anticancer therapy or subsequent surgery/procedure (whichever is first recorded) will not be used. All evaluable data will be classified as a clinically significant abnormal value or not. The criteria in the table below will be used.

Table 9.a Clinically Significant Abnormal Value Criteria for ECG Parameters

Abnormality	Criteria
QTcF Interval Prolongation (based on observed value)	500msec<
QTcF Interval Prolongation (based on change from baseline)	60msec<

9.2 Definition of Adverse Event of Clinical Interest

- ILD/Pneumonitis

PT_CODE (a)	PT_NAME (a)
10066728	Acute interstitial pneumonitis
10073344	Alveolar lung disease
10001881	Alveolar proteinosis
10001889	Alveolitis
10050343	Alveolitis necrotising
10080701	Autoimmune lung disease
10006448	Bronchiolitis
10076515	Combined pulmonary fibrosis and emphysema
10060902	Diffuse alveolar damage
10014952	Eosinophilia myalgia syndrome
10078117	Eosinophilic granulomatosis with polyangiitis
10014962	Eosinophilic pneumonia
10052832	Eosinophilic pneumonia acute
10052833	Eosinophilic pneumonia chronic
10081988	Hypersensitivity pneumonitis
10078268	Idiopathic interstitial pneumonia
10063725	Idiopathic pneumonia syndrome
10021240	Idiopathic pulmonary fibrosis
10082452	Immune-mediated pneumonitis
10022611	Interstitial lung disease

PT_CODE (a)	PT_NAME (a)
10025102	Lung infiltration
10081792	Lung opacity
10070831	Necrotising bronchiolitis
10029888	Obliterative bronchiolitis
10035742	Pneumonitis
10036805	Progressive massive fibrosis
10037383	Pulmonary fibrosis
10058824	Pulmonary necrosis
10061473	Pulmonary radiation injury
10061924	Pulmonary toxicity
10037457	Pulmonary vasculitis
10037754	Radiation alveolitis
10037758	Radiation fibrosis - lung
10037765	Radiation pneumonitis
10080547	Small airways disease
10052235	Transfusion-related acute lung injury

(a) MedDRA version 23.0

- Cardiac disorders

PT_CODE (a)	PT_NAME (a)
10063748	Electrocardiogram QT interval abnormal
10014387	Electrocardiogram QT prolonged
10024803	Long QT syndrome
10057926	Long QT syndrome congenital
10044066	Torsade de pointes
10047302	Ventricular tachycardia
10007515	Cardiac arrest
10049993	Cardiac death
10061592	Cardiac fibrillation
10007617	Cardio-respiratory arrest
10052464	Electrocardiogram repolarisation abnormality
10062314	Electrocardiogram U wave inversion
10057913	Electrocardiogram U wave present
10055032	Electrocardiogram U-wave abnormality
10024855	Loss of consciousness
10077361	Multiple organ dysfunction syndrome
10081980	Subacute kidney injury
10049418	Sudden cardiac death

PT_CODE (a)	PT_NAME (a)
10042434	Sudden death
10042772	Syncope
10047281	Ventricular arrhythmia
10047290	Ventricular fibrillation
10047294	Ventricular flutter
10065341	Ventricular tachyarrhythmia
10003665	Atrial septal defect acquired
10004780	Biopsy heart abnormal
10007509	Cardiac amyloidosis
10007572	Cardiac hypertrophy
10080569	Cardiac iron overload
10007604	Cardiac sarcoidosis
10057576	Cardiac septal hypertrophy
10007636	Cardiomyopathy
10048377	Cardiomyopathy acute
10007637	Cardiomyopathy alcoholic
10050111	Cardiomyopathy neonatal
10048610	Cardiotoxicity
10080484	Chagas' cardiomyopathy
10056370	Congestive cardiomyopathy
10012647	Diabetic cardiomyopathy
10014331	Ejection fraction abnormal
10050528	Ejection fraction decreased
10014961	Eosinophilic myocarditis
10083635	Giant cell myocarditis
10069658	HIV cardiomyopathy
10058222	Hypertensive cardiomyopathy
10020871	Hypertrophic cardiomyopathy
10048858	Ischaemic cardiomyopathy
10070909	Metabolic cardiomyopathy
10054122	Myocardial calcification
10028594	Myocardial fibrosis
10048849	Myocardial haemorrhage
10049813	Non-obstructive cardiomyopathy
10081007	Obesity cardiomyopathy
10049430	Peripartum cardiomyopathy
10037329	Pulmonary arterial wedge pressure increased
10038748	Restrictive cardiomyopathy
10075337	Right ventricular ejection fraction decreased

PT_CODE (a)	PT_NAME (a)
10066286	Stress cardiomyopathy
10074269	Tachycardia induced cardiomyopathy
10075043	Thyrotoxic cardiomyopathy
10083657	Toxic cardiomyopathy
10047299	Ventricular septal defect acquired
10068767	Viral cardiomyopathy
10077162	Abnormal precordial movement
10000533	Acquired cardiac septal defect
10063081	Acute left ventricular failure
10072744	Alcohol septal ablation
10003119	Arrhythmia
10003130	Arrhythmia supraventricular
10072066	Artificial heart implant
10003445	Ascites
10079340	Atrial enlargement
10048623	Atrial hypertrophy
10049785	Atrial pressure increased
10064539	Autoimmune myocarditis
10077819	Bendopnoea
10005736	Blood pressure diastolic abnormal
10005737	Blood pressure diastolic decreased
10005739	Blood pressure diastolic increased
10005746	Blood pressure fluctuation
10051128	Blood pressure inadequately controlled
10005757	Blood pressure systolic abnormal
10005758	Blood pressure systolic decreased
10005760	Blood pressure systolic increased
10007513	Cardiac aneurysm
10077454	Cardiac contractility modulation therapy
10081886	Cardiac device reprogramming
10079751	Cardiac dysfunction
10061808	Cardiac electrophysiologic study abnormal
10007554	Cardiac failure
10007556	Cardiac failure acute
10007558	Cardiac failure chronic
10007559	Cardiac failure congestive
10058479	Cardiac function test abnormal
10053453	Cardiac imaging procedure abnormal
10007576	Cardiac index abnormal

PT_CODE (a)	PT_NAME (a)
10007577	Cardiac index decreased
10007578	Cardiac index increased
10053440	Cardiac monitoring abnormal
10061026	Cardiac operation
10007595	Cardiac output decreased
10048974	Cardiac pseudoaneurysm
10059862	Cardiac resynchronisation therapy
10076898	Cardiac ventricular scarring
10053447	Cardiac ventriculogram abnormal
10053499	Cardiac ventriculogram left abnormal
10053444	Cardiac ventriculogram right abnormal
10007632	Cardiomegaly
10007646	Cardiothoracic ratio increased
10007649	Cardiovascular disorder
10007651	Cardiovascular function test abnormal
10008479	Chest pain
10008499	Chest X-ray abnormal
10057799	Computerised tomogram thorax abnormal
10011254	Coxsackie carditis
10011258	Coxsackie myocarditis
10056261	Cytomegalovirus myocarditis
10050905	Decreased ventricular preload
10052337	Diastolic dysfunction
10013002	Dilatation atrial
10013012	Dilatation ventricular
10013048	Directional Doppler flow tests abnormal
10013968	Dyspnoea
10050998	ECG signs of ventricular hypertrophy
10061593	Echocardiogram abnormal
10014363	Electrocardiogram abnormal
10061116	Electrocardiogram change
10081493	Electrocardiogram PR segment depression
10014663	Endocardial fibroelastosis
10075553	Enterovirus myocarditis
10067876	External counterpulsation
10078670	Gonococcal heart disease
10056409	Heart and lung transplant
10019314	Heart transplant
10019842	Hepatomegaly

PT_CODE (a)	PT_NAME (a)
10068359	Hyperdynamic left ventricle
10081004	Hypersensitivity myocarditis
10082606	Immune-mediated myocarditis
10082009	Implantable cardiac monitor replacement
10050900	Increased ventricular preload
10079904	Intracardiac pressure increased
10076213	Irregular breathing
10023533	Labile blood pressure
10067286	Left atrial dilatation
10051860	Left atrial enlargement
10082367	Left atrial volume abnormal
10082368	Left atrial volume decreased
10082369	Left atrial volume increased
10050043	Left ventricular dilatation
10049694	Left ventricular dysfunction
10060089	Left ventricular end-diastolic pressure decreased
10050581	Left ventricular enlargement
10024119	Left ventricular failure
10052348	Left ventricular heave
10081792	Lung opacity
10066391	Lupus myocarditis
10078417	Lyme carditis
10083143	Magnetic resonance imaging thoracic abnormal
10054123	Malarial myocarditis
10048294	Mental status changes
10028212	Multiple gated acquisition scan abnormal
10058440	Myocardiac abscess
10075211	Myocardial necrosis marker increased
10028606	Myocarditis
10065218	Myocarditis bacterial
10065219	Myocarditis helminthic
10066857	Myocarditis infectious
10028612	Myocarditis meningococcal
10059026	Myocarditis mycotic
10064550	Myocarditis post infection
10028615	Myocarditis septic
10028616	Myocarditis syphilitic
10028617	Myocarditis toxoplasmal
10058735	Myoglobinaemia

PT_CODE (a)	PT_NAME (a)
10028629	Myoglobinuria
10029446	Nocturia
10030095	Oedema
10031127	Orthostatic hypotension
10033557	Palpitations
10061330	Papillary muscle disorder
10059164	Papillary muscle haemorrhage
10076389	Radiation myocarditis
10067282	Right atrial dilatation
10058227	Right atrial enlargement
10067283	Right atrial pressure increased
10064195	Right ventricle outflow tract obstruction
10074222	Right ventricular dilatation
10050582	Right ventricular enlargement
10070955	Right ventricular heave
10060237	Right ventricular systolic pressure decreased
10061501	Scan myocardial perfusion abnormal
10078218	Surgical ventricular restoration
10076976	Systolic anterior motion of mitral valve
10071436	Systolic dysfunction
10045413	Ultrasound Doppler abnormal
10067285	Vascular resistance pulmonary increased
10052371	Ventricular assist device insertion
10059056	Ventricular dysfunction
10059162	Ventricular dyskinesia
10071186	Ventricular dyssynchrony
10079339	Ventricular enlargement
10056472	Ventricular hyperkinesia
10047295	Ventricular hypertrophy
10050510	Ventricular hypokinesia
10075291	Ventricular remodelling
10047470	Viral myocarditis
10079016	Wall motion score index abnormal
10003658	Atrial fibrillation
10003662	Atrial flutter
10071666	Atrial parasystole
10003668	Atrial tachycardia
10082343	Congenital supraventricular tachycardia
10082089	Frederick's syndrome

PT_CODE (a)	PT_NAME (a)
10074640	Junctional ectopic tachycardia
10040752	Sinus tachycardia
10042602	Supraventricular extrasystoles
10065342	Supraventricular tachyarrhythmia
10042604	Supraventricular tachycardia
10081099	Acute cardiac event
10051592	Acute coronary syndrome
10000891	Acute myocardial infarction
10002388	Angina unstable
10005472	Blood creatine phosphokinase MB abnormal
10005474	Blood creatine phosphokinase MB increased
10011084	Coronary artery embolism
10011086	Coronary artery occlusion
10053261	Coronary artery reocclusion
10011091	Coronary artery thrombosis
10059025	Coronary bypass thrombosis
10075162	Coronary vascular graft occlusion
10069167	Kounis syndrome
10028596	Myocardial infarction
10028602	Myocardial necrosis
10051624	Myocardial reperfusion injury
10072186	Myocardial stunning
10033697	Papillary muscle infarction
10079319	Periprocedural myocardial infarction
10066592	Post procedural myocardial infarction
10058144	Postinfarction angina
10049768	Silent myocardial infarction
10058268	Troponin I increased
10058267	Troponin increased
10058269	Troponin T increased

(a) MedDRA version 23.0

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Biostatistics Approval	19-Jan-2022 15:24 UTC