STATISTICAL ANALYSIS PLAN

YH25448-201

A PHASE I/II, OPEN-LABEL, MULTICENTER STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND ANTI-TUMOR ACTIVITY OF YH25448 IN PATIENTS WITH EGFR MUTATION POSITIVE ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V4.0 and Mock-up TFL (both dated 15 Apr 2021) for Protocol YH25448-201.

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	15June2017	PPD	Not Applicable – First Version
2.0	17Jan2019		All Document. - Updated to SAP based on protocol version 8.0 1. Added definitions for brain metastatic analysis set -Brain Metastatic Full Analysis Population -Brain Metastatic Evaluable for Response Population 2. Deleted definitions Brain Metastasis Cohort in Part C 3. Added Integrated analysis
3.0	21Nov2019		All Document. - Updated to SAP based on protocol Eng version 7.0 1. Added analysis Parts C and D 2. Added Race variable in Section 10 (Only for Part D and Integrated analysis) 3. Added Time point response - Table 1: Visit Response (extracranial and intracranial disease) 4. Change the standard for causality assessment 5. Deleted TEAEs of Special Interest

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
4.0		PPD	All Document. - Updated to SAP based on protocol Eng version 9.0 1. Added General description for primary database lock in Section 3.1 2. Added Final analyses after the primary database lock in Section 4.4 3. Deleted Sensitivity analyses for Part C in Section 4.3 4. Excepted of Part D in integrated analyses.

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LIST OF ABBREVIATIONS

AUC_{0-24}	Area under the Plasma Concentration-Time Curve from Zero to 24 Hours
AUC_{inf}	Area under the Plasma Concentration-Time Curve from Zero to Infinity
AUC_{ss}	Area under the Plasma Concentration-Time Curve from Zero to the End of the Dosing Interval
AUC_t	Area under the Plasma Concentration-Time Curve from Zero to the Time of the Last Quantitative Concentration
BLQ	Below Limit of Quantification
C_{CSF}	CSF Concentration
C_{DX}	Trough Plasma Concentration on Day X
CL/F	Apparent Plasma Clearance
CL_{ss}/F	Apparent Plasma Clearance at Steady State
C_{max}	Maximum Plasma Concentration
$C_{max,ss}$	Maximum Plasma Concentration at Steady State
CR	Complete Response
CSF	Cerebrospinal Fluid
CSR	Clinical Study Report
CV	Coefficient of Variation
DCR	Disease Control Rate
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
DoR	Duration of Response
EF	Emotional Functioning
EGFRm+	Epidermal Growth Factor Receptor Mutation Positive
HRQoL	Health Related Quality of Life
ICF	Informed Consent Form
ICR	Independent Central Review
IP	Investigational Product
LLOQ	Lower Limit of Quantification

MAD	Maximum Absorbable Dose
MedDRA	Medical Dictionary for Regulatory Activities
MR	Metabolic Ratio
MR_{ss}	Metabolic Ratio at Steady State
MTD	Maximum Tolerated Dose
NA	Not Applicable
ND	Not Detected
NE	Not Evaluable
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PFS	Progression Free Survival
PK	Pharmacokinetic
PR	Partial Response
PRO	Patient Reported Outcomes
PT	Preferred Term
R_{ac}	Accumulation Ratio
RECIST	Response Evaluation Criteria in Solid Tumors
RS	Raw Score
SAP	Statistical Analysis Plan
SD	Stable Disease
SOC	System Organ Class
SRC	Safety Review Committee
STD	Standard Deviation
$t_{1/2}$	Apparent Terminal Elimination Half-life
TKI	Tyrosine Kinase Inhibitor
TL	Target Lesion
T_{max}	Time to Reach C_{max}
$T_{max,ss}$	Time to Reach $C_{max,ss}$
TSM	Tumor Size Measurement

Vd/F	Apparent Volume of Distribution
WHO-DDE	World Health Organization Drug Dictionary Enhanced
λ_z	Apparent Terminal Elimination Rate Constant

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol YH25448-201. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol Eng version 9.0, dated 2021-01-08.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

Parts A, B and C:

To evaluate the safety, tolerability and efficacy of YH25448 when given orally to patients with EGFR Mutation Positive (EGFRm+) locally advanced or metastatic NSCLC.

Part D (Applies to patients enrolled outside of Korea only):

To evaluate the safety, tolerability, and pharmacokinetics (PK) of YH25448 when given orally to patients with EGFR Mutation Positive (EGFRm+) locally advanced or metastatic NSCLC.

2.2. SECONDARY OBJECTIVES

Parts A, B and C:

To define the maximum tolerated dose (MTD), if possible, a dose/exposure predicted to result in anti-tumor activity and maximum absorbable dose (MAD).

To characterize the pharmacokinetic (PK) profiles of YH25448 and its potential metabolites, including M7, following a single oral dose and at steady state.

Dose Escalation and Expansion phases: To obtain a preliminary assessment of the anti-tumor activity of YH25448 by evaluation of objective response rate (ORR), duration of response (DoR), disease control rate (DCR), tumor shrinkage and progression free survival (PFS) using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

Dose Extension phase: To obtain additional assessments of the anti-tumor activity of YH25448 by evaluation of DoR, disease control rate (DCR), tumor shrinkage and PFS using RECIST 1.1 as assessed by an independent central review (ICR) of radiological information and overall survival (OS).

Part D:

To characterize the PK profiles of potential YH25448 metabolites in plasma, including M7, following a single oral dose and at steady state.

To obtain additional assessments of the anti-tumor activity of YH25448 by evaluation of objective response rate (ORR), duration of response (DoR), disease control rate (DCR), tumor shrinkage and progression free survival (PFS) using RECIST 1.1 as assessed by investigator review of radiological information and overall survival (OS).

2.3. EXPLORATORY OBJECTIVES

Parts, A, B and C

To collect and store plasma for potential exploratory research of blood born biomarkers into factors that may influence development of NSCLC and/or response to YH25448 (where response is defined broadly to include efficacy, tolerability or safety).

To collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes/genetic variation that may influence PK or response (i.e. absorption, distribution, metabolism, excretion, safety, tolerability and efficacy) to YH25448 treatment and or susceptibility to cancers.

To collect and store diagnostic tumor sample and any fresh tumor biopsies for potential future exploratory research into factors that may influence development of NSCLC and/or responses to YH25448 (where response is defined broadly to include efficacy, tolerability or safety).

To collect patient reported outcomes (PRO) data to explore disease-related symptoms and health related quality of life (HRQoL).

To assess the relationship between PK and selected efficacy, pharmacodynamic and/or safety endpoints, where deemed appropriate.

To characterize the PK profiles of YH25448 and its potential metabolites, including M7, in cerebrospinal fluid (CSF).

To collect and store residual CSF for potential exploratory research of factors that may influence development of NSCLC and/or response to YH25448 (where response is defined broadly to include efficacy, tolerability or safety).

Part D

To collect deoxyribonucleic acid (DNA) for exploratory research into genes/genetic variation that may influence PK or response (i.e. absorption, distribution, metabolism, excretion, safety, tolerability and efficacy) to YH25448 treatment and or susceptibility to cancers. The specific objective of the pharmacogenetic assessment is to investigate genetic variants of the Glutathione S-Transferase Mu 1 (GSTM1) genotypes affecting the disposition of YH25448 and to understand the correlation of GSTM1 genetic variants with PK and safety and tolerability.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

Parts A, B, and C

This is a phase I/II, open-label, multicenter study of YH25448 administered orally in patients with EGFRm+ NSCLC with or without asymptomatic brain metastasis. The study design allows an escalation of dose with intensive safety monitoring to ensure the safety of the patients. It is possible for additional dose levels to be added during the course of the study.

Part D

This is a phase I/II, open-label, multicenter study of YH25448 administered orally in patients with EGFRm+ NSCLC with or without asymptomatic brain metastasis. YH25448 will be given to patients outside Korea, including Caucasians, at the current RP2D of 240 mg and 320 mg in order to evaluate safety, tolerability, efficacy (including tumor response) and PK in patients outside of Korea.

A cycle of study treatment will be defined as 21 days of continuous dosing and the evaluation of measurable lesion as per RECIST 1.1 will be performed at every 2 cycles. After the primary database lock, radiological disease evaluations are not required and may be performed at the discretion of the investigator in accordance with local standard of care.

There are four parts to this study. Part A, Dose escalation phase, Part B, Dose expansion phase, Part C, Dose extension phase and Part D, patients outside Korea. Please refer Figure 1 for diagram of study design.

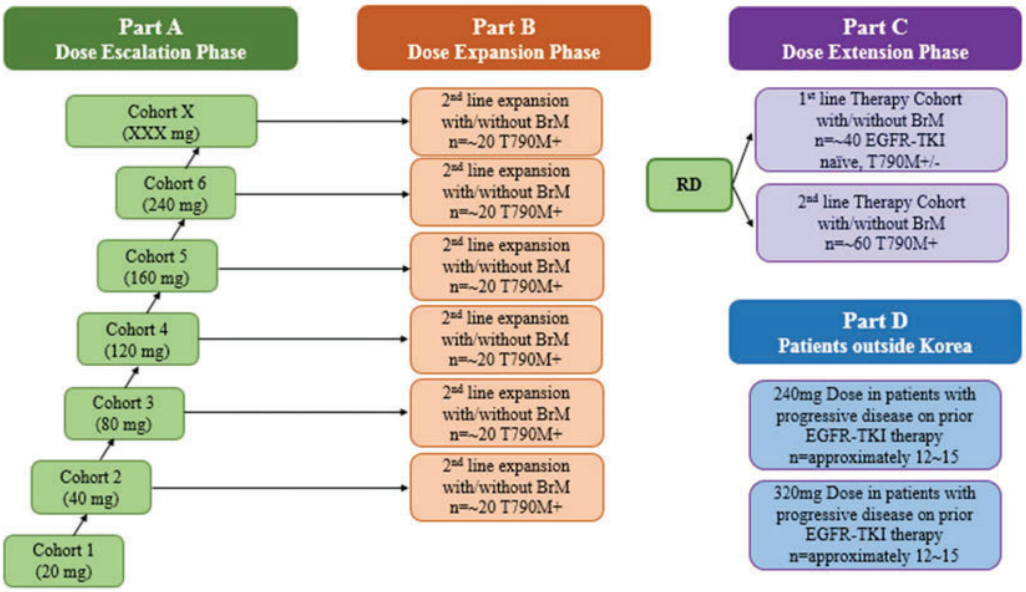

Figure 1 Diagram of study design

RD : recommended dose

BrM : brain metastasis

3.1.1. PART A: DOSE ESCALATION PHASE

The part A will determine the MTD or MAD of YH25448 for max. 6 patients of each cohort based upon assessment of the safety, tolerability and PK data collected during the first 21 days of daily dosing in patients who experienced clinical benefit from EGFR TKIs followed by progressive disease while on continuous treatment with the authorized EGFR TKIs prior to enrolling in the study.

At least 3 and up to 6 patients for evaluating DLT will be required for each cohort. It is possible that an additional dose cohort is evaluated as necessary following dose escalation or dose de-escalation.

Please refer to the protocol for the dose escalation and de-escalation scheme.

For PK assessment of single and multiple doses, patients will receive a single dose on Day 1 Cycle 0 and then, after 7±2 days washout, multiple dosing, once daily will be initiated. PK blood samples will be collected over 60 hours after single dose. In the first cohort administration of the first dose will be separated from the start of dosing of the subsequent patients by at least 7 days for the first patient. Dosing frequency (e.g. bid) may be adjusted during the study on the basis of emerging safety and PK data. Trough plasma concentrations will be measured at each visit during Cycle 1, and PK evaluation at steady state will be performed over 24 hours after the first administration in Cycle 2.

3.1.2. PART B: DOSE EXPANSION PHASE

Part B will be conducted to assess safety, tolerability, efficacy and PK of YH25448 for approximately 20 evaluable patients per each cohort with T790M+ on the basis of central confirmed T790M mutation result who have experience in the authorized EGFR TKIs therapy, followed by progressive disease prior to enrolling in the study regardless of whether BrM has occurred or not.

Trough plasma concentrations will be measured at each visit during Cycle 1, and PK evaluation at steady state will be performed over 24 hours after the first administration in Cycle 2.

Each dose cohort of part B will be started to enroll the patient after confirmation of safety data for each corresponding dose cohort of part A. Safety review committee (SRC) will determine the change of dose level and decide to quit patients enrollment based on emerging data from expansion phases.

3.1.3. PART C: DOSE EXTENSION PHASE

Once the MTD or RD is reached additional 2 cohorts of 100 evaluable patients will be enrolled to assess the efficacy, safety and tolerability of YH25448. Through plasma concentrations for PK evaluation will be measured at each visit during Cycle 1.

1) 2nd line therapy Cohort

The efficacy and the tolerability of YH25448 will be assessed for approximately 60 patients with T790M+ who have received the authorized EGFR TKIs treatments, and also progressive disease must be confirmed after any of their recent treatment regardless of BrM occurrence.

2) 1st line therapy Cohort

Approximately 40 patients with EGFRm+ NSCLC who are EGFR TKI-naïve regardless of BrM occurrence will be enrolled to assess the efficacy and tolerability of YH25448.

3.1.4. PART D: PATIENTS OUTSIDE KOREA

The goal of Part D is to evaluate the safety, tolerability, efficacy and PK of YH25448 at the 240 mg and 320 mg dose levels in patients enrolled outside Korea. Approximately 12-15 patients outside Korea will be enrolled at each dose level to provide a minimum of 6 Caucasian patients with evaluable PK.

3.2. SCHEDULE OF EVENTS

Schedule of events can be found in Section 6.1 of the Protocol.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

As for left ventricular ejection fraction(LVEF) measured by echocardiography or MUGA scan, additional analyses of minimum post-baseline LVEF value, maximum LVEF change from baseline value and proportion of patients with LVEF of <-10 % point change from baseline and minimum post baseline value <50% were performed.

4. PLANNED ANALYSES

4.1. SUBGROUP ANALYSIS

The subgroup analysis of integrated analysis is planned for T790M+, T790M- and BrM population.

4.2. INTERIM ANALYSIS

No interim analysis is planned for this study.

4.3. SENSITIVITY ANALYSIS

The same methods of analysis will be applied to analyze ORR, DoR, DCR, tumor shrinkage and PFS based on the RECIST data assessed by the investigator as well as by ICR. In Part C, the same methods of analysis will be applied to analyze YH25448 anticancer effects (PFS, ORR, DoR, DCR and tumor shrinkage) for all patients with a positive EGFR mutation status in the central and / or local testing.

4.4. FINAL ANALYSIS

After the primary database lock, there will be performed for Overall Survival (OS) and Safety Outcomes in the final analyses.

All final, planned analyses identified in this SAP will be performed by LSK Global PS Biostatistics following sponsor authorization of this SAP and database lock.

This SAP will cover analyses for parts A, B, C and part D.

Pharmacokinetic analyses for parts A, B, C and part D will be discussed in this SAP. PK analysis will be performed by a clinical PK scientist at Yuhan.

Results from all other exploratory objectives except patient report outcome will be reported separately

from the clinical study report (CSR).

The following topics will not be discussed in this document:

- Metabolite identification
- Biomarker data
- Pharmacogenetics
- Diagnostic of tumor samples

4.5. INTEGRATED ANALYSIS

There will be performed integrated analyses for 2nd line therapy cohorts (Parts A, B and C-2nd) in the overall integrated analysis sets.

For the efficacy outcome, there will be analyzed to integrated analysis set(except Part D) as well as subgroup for T790M+, T790M- and BrM population.

Integrated analysis will be performed in the following depending on DB freezing or DB locking:

- 1st DB Freezing(after cycle 4 of the last patient in Part C 1st line) : Parts A and B
- 2nd DB Freezing(after cycle 6 of the last patient in Part C 2nd line) : Parts A, B and C-2nd line
- Primary and Final DB Locking : Parts A, B and C-2nd line

5. ANALYSIS SETS AND PROTOCOL DEVIATIONS

Unless otherwise specified in the document, all summaries will be presented by assigned dose level.

All patients will be presented according to their initial assigned dose level regardless of any dose adjustment during study conduct.

5.1. SCREENED POPULATION

All patients who have signed a main written informed consent form (ICF) and received a screening number.

5.2. SAFETY ANALYSIS POPULATION

All patients who received at least one dose of investigational product (IP). All safety analyses except for DLT summaries will be based on the safety analysis population.

5.3. Dose Limiting Toxicity (DLT) Evaluable Patients (Only Part A)

The dose limiting toxicity (DLT) evaluable patients comprise all safety analysis population who are evaluable for DLT assessment.

An evaluable patient is defined as a patient that has received YH25448 and meets one of the following criteria:

- has experienced a DLT during the single dose period or the first 21 days of continuous dosing.
- has completed safety evaluation requirement during the single dose period and over the first 21 days of continuous dosing.
- has taken study drugs over 14 days during the first 21 days of continuous dosing.

5.4. Evaluable for Response Population

All patients in the safety analysis population who have a baseline RECIST 1.1 assessment whose tumor EGRF mutation status was confirmed via a central testing. Central testing results must match the cohort to which they were assigned. For Part D, all patients in the safety analysis population who have a baseline RECIST 1.1 assessment (no central testing of EGFR mutation status is required).

5.5. Brain Metastatic Full Analysis Population

All patients in the evaluable for response population who have a measurable and/or unmeasurable intracranial lesion at baseline by ICR.

All patients in the evaluable for response population who have a measurable and/or unmeasurable intracranial lesion at baseline by Investigator.

5.6. Brain Metastatic Evaluable for Response Population

All patients in the brain metastatic full analysis population who have at least one measurable intracranial lesion at baseline by ICR.

All patients in the brain metastatic full analysis population who have at least one measurable intracranial lesion at baseline by Investigator.

5.7. Pharmacokinetic Analysis Population

All patients who have at least one measurable concentration collected post-dose. All adverse events, protocol deviations or incomplete dosing interval (i.e. within 14 hour- or over 34 hour-interval between two dosing on Day 21, Cycle 1 and Day 1, Cycle 2) that occur during the PK evaluation period will be considered for their severity and impact on PK and will be taken into consideration with Yuhan Study Physician and Clinical PK Scientist when patients are assigned to analysis populations.

5.8. PROTOCOL DEVIATIONS

Protocol deviations describe how close the study has been conducted according to the protocol as expected per GCP. None of the deviations will lead to any patients being excluded from any of the analysis sets (with exception of the PK analysis population, if the deviation is considered to impact upon PK). If the deviations are serious enough to have the potential to impact key efficacy endpoints, additional summaries might be generated.

Important protocol deviations are protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a patient's rights, safety, or well-being.

The details of important protocol deviations will be identified by the study team, prior to database lock of the study. The following are examples of important protocol deviations:

- Patients that are dosed on the study despite not satisfying the inclusion criteria;
- Patients that develop withdrawal criteria whilst on the study but are not withdrawn;
- Patients that receive an incorrect dose;
- Patients that receive an excluded exhibited concomitant medication;
- Deviation from GCP.

6. GENERAL CONSIDERATIONS

6.1. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date, and will be used to show start/ stop day of assessments and events.

Reference start date is defined as the day of the first dose of study medication, (Day 1 is the day of the first dose of study medication), and will appear in every listing where an assessment date or event date appears.

- If the date of the event is on or after the reference date then:

Study Day = (date of event – reference date) + 1.

- If the date of the event is prior to the reference date then:

Study Day = (date of event – reference date).

6.2. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments).

If the last non-missing measurement and the reference start date coincide, that measurement will be considered pre-baseline, but Adverse Events (AEs) and medications commencing on the reference start date will be considered post-baseline.

6.3. END OF TREATMENT

End of treatment reasons and treatment discontinuation date are captured on CRF page "discontinuation summary".

Patients who complete or prematurely discontinue the study need to return to the study site for a follow-up within 7 days after the last dose of YH25448. Measurements obtained during this visit will be considered as the end of treatment assessment.

A 28-day follow-up visit will be scheduled 28 days (+7 days) after end of treatment visit.

Patients who discontinued study drug without disease progression will undergo tumor assessment every 2 cycles (±7) until disease progression. For BrM patients, patients who have confirmed disease progression only in extracranial lesions will continue to undergo RECIST 1.1 assessment every 2 cycles for intracranial lesion until progression.

The end of the study is defined as the last visit of the last patient undergoing the study.

6.4. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries, but will contribute to the worst case summaries.

In the case of a retest (visit-specific unscheduled visit number assigned), the latest non-missing measurement among all scheduled and unscheduled measurements for that visit will be used for by-visit summaries.

Early termination data of patients prematurely discontinued from study treatment will be presented together with the end of treatment assessment for study treatment completers.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

6.5. WINDOWING CONVENTIONS

Please refer Table 8, Table 9, Table 10 and Table 11 of protocol for study visit window.

6.6. STATISTICAL TESTS

No statistical tests will be performed.

Unless otherwise specified in the description of the analyses, two sided 95% confidence intervals will be used.

6.7. COMMON CALCULATIONS

For quantitative measurements, change from baseline and % change from baseline will be calculated as:

- Test Value at Visit X – Baseline Value
- (Test Value at Visit X – Baseline Value)/Baseline Value * 100

The time from Date of Event A to Date of Event B (years) is calculated as:

- (Date of Event B - Date of Event A + 1)/365.25.

The time from Date of Event A to Date of Event B (months) is calculated as:

- (Date of Event B - Date of Event A + 1)/30.4375.

The time from Date of Event A to Date of Event B (weeks) is calculated as:

- (Date of Event B - Date of Event A + 1)/7.

First day of study treatment will be applied as:

- Parts A and D: First date of single dosing (Cycle 0 – Day 1)
- Parts B and C: First date of multiple dosing (Cycle 1 – Day 1)
- Integrated: First date of multiple dosing (Cycle 1- Day 1).

6.8. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4 or higher.

PK analyses will be conducted using Phoenix WinNonlin version 6.4 or higher (Pharsight Corporation).

7. STATISTICAL CONSIDERATIONS

7.1. SAMPLE SIZE

Approximately 30 patients with EGFRm+ NSCLC who had progressed following prior EGFR TKIs therapy will be enrolled in part A. The total number of patients will depend upon the number of dose escalations necessary.

Approximately 20 evaluable patients with T790M+ mutation NSCLC regardless of brain metastasis (2nd line expansion with/without BrM) who had progressed following prior EGFR TKIs therapy will be enrolled per dose level in part B. The total number of patients will depend upon the number of dose cohorts.

A total of 60 evaluable patients is required for the 2nd line therapy cohort in Part C.

A total of 40 evaluable patients is required for the 1st line therapy cohort in Part C.

Approximately 12~15 patients outside Korea will be enrolled at each 240 mg and 360 mg dose level to provide a minimum of 6 Caucasian patients with evaluable PK in part D. Although enrollment will not be based on race, it is expected that approximately 80% of patients will be Caucasian.

7.2. MULTICENTER STUDIES

This study will be conducted by multiple centers and center pooling will be carried out for use in analyses for this study.

7.3. MISSING DATA

Unless otherwise specified in this SAP, all data will be evaluated as observed, and no imputation method for missing values will be used.

Partial dates, which are not to be imputed according to the SAP, will be presented in the format like "_____YYYY". If values are imputed according to the SAP, imputed values will be presented in patient data listings and imputed information will be flagged.

Missing statistics, e.g. when they cannot be calculated, should be presented as "-". For example, if n=1, the measure of variability (e.g. standard deviation) cannot be computed and should be presented as "-".

7.4. HANDLING OF INCOMPLETE DATES

Incomplete dates (date of informed consent, date of birth) for the calculation of age will be imputed as follows:

- In case of missing day for at least one date, but month and year available for both dates: the day of informed consent and the day of birth will be set to 1.
- In case of missing month for at least one date, but year available for both dates, the day and the month of informed consent and the day and month of birth will be set to 1.

For adverse events, prior or concomitant medications, incomplete start dates and/or stop dates will be imputed. When the start date and the stop date are both incomplete for a patient, the start date will be imputed first. If the stop date is complete and the imputed start date using rules below is after the stop date, the start date will be imputed using the stop date.

Incomplete Start Date:

Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of IP, the month and day of the first dose of IP will be assigned to the missing fields
- If the year of the incomplete start date is before the year of the first dose of IP, December 31 will be assigned to the missing fields
- If the year of the incomplete start date is after the year of the first dose of IP, January 1 will be assigned to the missing fields

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of IP, the day of the first dose of IP will be assigned to the missing day
- If either the year of the incomplete start date is before the year of the date of the first dose of IP or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of IP, the last day of the month will be assigned to the missing day.
- If either the year of the incomplete start date is after the year of the date of the first dose of IP or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of IP, the first day of the month will be assigned to the missing day

Incomplete Stop Date:

If the imputed stop date using rules below is before the start date (imputed or non-imputed start date), the imputed stop date will be equal to the start date.

Missing month and day

- If the year of the incomplete stop date is the same as the year of the last dose of IP, the month and day of the last dose of IP will be assigned to the missing fields
- If the year of the incomplete stop date is before the year of the last dose of IP, December 31 will be assigned to the missing fields
- If the year of the incomplete stop date is after the year of the last dose of IP, January 1 will be assigned to the missing fields

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the last dose of IP, the day of the last dose of IP will be assigned to the missing day
- If either the year of the incomplete stop date is before the year of the date of the last dose of IP or if both years are the same but the month of the incomplete stop date is before the month of the date of the last dose of IP, the last day of the month will be assigned to the missing day
- If either the year of the incomplete stop date is after the year of the last dose of IP or if both years are the same but the month of the incomplete stop date is after the month of the last dose of IP, the first day of the month will be assigned to the missing day

7.5. HANDLING OF INCOMPLETE TARGET LESION DATA

Rounding of Target Lesion (TL) data:

For Calculation of PD and PR for TLs percentage changes from baseline and previous minimum should be rounded to 1 decimal place before assigning a target lesion response. For example 19.95% should be rounded to 20.0% but 19.94% should be rounded to 19.9%.

Missing TL data:

- All TL data missing at a visit

If all target lesion measurements are missing then the target lesion visit response is Not Evaluable (NE). The overall visit response will also be NE, unless there is a progression of non-target lesions or new lesions, in which case the response will be PD.

- Some TL data missing at a visit (scaling-up rule)

  - If >1/3 of target lesion measurements are missing then target lesion response will be NE, unless the sum of diameters of non-missing target lesion would result in PD (i.e. if using a value of 0 for missing lesions, the sum of diameters has still increased by >20% or more compared to nadir and the sum of target lesions has increased by 5mm from nadir).

  - If ≤1/3 of the target lesion measurements are missing then the results will be scaled up (based on the nadir sizes) to give an estimated sum of diameters and this will be used in calculations; this is equivalent to comparing the visit sum of diameters of the non-missing lesions to the nadir sum of diameters excluding the lesions with missing measurements.

  CR will not be allowed as a TL response for visits where there is missing data. Only PR, SD or PD (or NE) could be assigned as the TL visit response in these cases. However, for visits with ≤1/3 lesion assessment not recorded the scaled up sum of TLs diameters will be included when defining the nadir value for the assessment of progression.

8. OUTPUT PRESENTATIONS

Appendix 1 shows conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures and listings to be provided by LSK Global PS statistician.

Continuous variables will be summarized using descriptive statistics:

- Number of patients (n)
- Mean
- Median
- Standard deviation (STD)
- Ranges (minimum, Q1, Q3, maximum).

For continuous data, mean, standard deviation and median will be rounded to 1 additional decimal place compared to the original data. Minimum and maximum will be displayed with the same accuracy as the original data.

Qualitative variables will be summarized by count(s) and percentages (%). Unless otherwise stated, the calculation of percentages will be based on the total number of patients included in the relevant analysis set. For categorical data, percentages will be rounded to 1 decimal place.

9. DISPOSITION AND WITHDRAWALS

All patients who provide main ICF will be accounted for in this study.

Patient disposition of each study stage (screening phase, treatment discontinuation, and end of study), and corresponding the reasons will be presented by dose level and overall when applicable. The number of patients that receive at least one treatment (safety analysis population), the number of patients that are still on treatment, and the number of patients that are still in follow up at data cut-off will be provided. Relevant information will be recorded on CRF pages "Screening Pass/Fail Status", "Discontinuation" and "End of Study".

The number of patients for all analysis sets will be summarized by dose level and overall.

A frequency table per reason of important protocol deviations will be provided. All protocol deviations will be listed for the safety analysis population.

Listings for patient disposition, patient completion, and protocol deviations will be provided with relevant information. Reasons for discontinuation of IP will be listed including the study day of treatment discontinuation.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the safety analysis population and summarized by dose level and overall.

No statistical testing will be carried out for demographic or other baseline characteristics.

The following demographic and other baseline characteristics will be reported for this study:

- Age (years) - calculated relative to date of consent
- Age categories: < 55 years, ≥ 55 years (55-64, 65-74 years, and ≥ 75 years)
- Sex: Male, Female
- Ethnicity: Asian, Hispanic or Latino, African-American, Other
- Race : Asian,American Indian or Alaska Native, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other (Only for Part D)
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- ECOG performance status: 0, 1
- Smoking status: Never, Former, Current, Not Reported
- Pack Year
- Extent of disease
    - NSCLC Pathology Classification: Adenocarcinoma. Adeno-squamous Carcinoma, Large cell carcinoma, Other
    - Time since First Diagnosis (years)
    - Age at diagnosis (years)
    - EGFR mutation result: Positive (L858R, Exon19Del, G719X, L861Q, Other), Negative, Unknown
    - T790M mutation status by cobas® central test: Positive, Negative, Unknown

- Target lesions: Lymph Node only, Non-Lymph Node only, Both
- Non-target lesions: Yes, No
- TNM Stage
- Metastatic lesion at M1: Brain, Liver, Adrenal, Bone, Other
- Number of organ involved: 1, 2, 3, 4, 5, >5
- Stage (by AJCC 7th Edition)

A listing of demographic characteristics with relevant information will be provided.

10.1. DERIVATIONS

- Pack Year = Packs smoked per day * Years as a smoker.
- Time since First Diagnosis (years) = (date of first study medication administration – first date of diagnosis)/365.25
- Age at diagnosis (years) = year of diagnosis – years of Birthday – 1,

If, date of diagnosis (mm/dd) < date of birthday (mm/dd)

= year of diagnosis – year of birthday,

If, date of diagnosis (mm/dd) ≥ date of birthday (mm/dd)

11. MEDICAL/SURGICAL HISTORY

Medical/surgical history information will be presented for the safety analysis population and summarized by dose group. Information will be obtained from the "Medical/Surgical History"

Medical/surgical history will be coded using the latest available version of Medical Dictionary for Regulatory Activities (MedDRA) with Preferred Term (PT) (decreasing frequency) as event category and MedDRA System Organ Class (SOC) (decreasing frequency) as summary category.

Medical/surgical history will be presented by SOC and PT. Each patient will be counted only once within each PT or SOC. In addition, a listing of medical/surgical history with relevant information will be provided.

12. CONCOMITANT MEDICATIONS AND PROCEDURES

12.1. PRIOR AND CONCOMITANT MEDICATIONS

Prior and concomitant medications will be presented for the safety analysis population and summarized by dose group. Prior and concomitant medications are captured on CRF page "Concomitant Medications".

Prior medication is defined as any medication taken within the period from 28 days before intake of IP. Concomitant medication is defined as any medication taken during the treatment and 28-day follow-up

period.

Prior and concomitant medications will be coded using latest version of World Health Organization Drug Dictionary Enhanced (WHO-DDE). ATC level 1, ATC level 3, and preferred name will be used for coding.

Prior and concomitant medications will be summarized separately by ATC level 1, ATC level 3, and preferred name. A listing will be provided with relevant information for prior and concomitant medications for the safety analysis population.

12.2. CONCOMITANT PROCEDURES

Concomitant procedures are captured on CRF page "Concomitant Procedures". The latest available version of MedDRA with SOC/PT will be used for coding.

Concomitant procedures will be listed for the safety analysis population.

13. PRIOR ONCOLOGY THERAPIES

Prior oncology therapies are collected under "Prior Cancer Radiotherapy", "Prior Cancer Chemotherapy", and "Prior Cancer-Related Surgeries/Procedures" eCRF pages. Prior cancer chemotherapy will be coded using latest version of World Health Organization Drug Dictionary Enhanced (WHO-DDE). The latest available version of MedDRA with SOC/PT will be used for prior cancer-related surgeries/procedures coding.

The number of patients in each of the following anti-cancer therapy categories will be tabulated for the safety analysis population:

- Patients with at least one type of previous anti-cancer treatment (i.e. radiotherapy, chemotherapy or surgery/procedure)
- Patients with at least one previous anti-cancer radiotherapy
    - Time from last radiotherapy to study entry (months)
    - Site of prior radiotherapy: Bone, Skin, …, Other
- Patients with at least one prior cancer chemotherapy
    - Prior lines of systemic therapy: 0, 1, ≥ 2
    - Regimen name
        - EGFR TKI: Gefitinib, Erlotinib, Afatinib, Dacomitinib …
        - Platinum based: Cisplatin, Carboplatin, …
        - Other regimens: …
    - Duration of last chemotherapy (months)

- Time from end of last therapy to study entry (months)
- Numbers of Prior EGFR-TKIs
- Immediate prior EGFR-TKI: Yes (<30 days, ≥30days), No, Missing
- Duration of most recent prior EGFR TKI: <6 months, ≥6months

- Patients with at least one prior cancer-related surgery/procedure

Prior oncology therapies will be listed for the safety analysis population.

13.1. DERIVATIONS

- When no other chemotherapy was used before treatment started, the EGFR TKI is also classified as immediate prior EGFR TKI.
- Immediate prior EGFR-TKI (days) = (first date of study medication administration – end date of Immediate prior EGFR TKI)
- Time from last radiotherapy to study entry (months) = (first date of study medication administration - end date of last radiotherapy)/30.4375
- Duration of last chemotherapy (months) = (end date of last chemotherapy – start date of last chemotherapy + 1)/30.4375
- Time from end of last therapy to study entry (months) = (first date of study medication administration - end date of last therapy)/30.4375
- Duration of most recent prior EGFR TKI (months) = (end date of most recent prior EGFR TKI – start date of most recent prior EGFR TKI + 1)/30.4375

14. STUDY MEDICATION COMPLIANCE AND EXPOSURE

The extent of compliance and exposure to study medication will be presented for the safety analysis population. Study medication administration will be taken from the eCRF "Dispense and Return Study Medication" and "Dose with YH25448" form.
The following summary table will be provided by dose level and overall:

- Duration of therapy (months)
- Number of patients treated by cycle
- Cumulative dose (mg)
- Relative dose intensity (RDI) (%) as continue variable, also categorized as >110%, >100-110%, >90-100%, >80-90%, >60-80%, ≤60%.
- The number of patients with at least one dose interruption and at least one dose reduction will be presented for Cycle 1 (from first dosing day to day 21 of multiple dosing) and the whole study.
- Frequency of dose interruptions

- Maximum duration of dose interruption (days)
- Frequency of dose reduction

Summary of exposure to study drug was analyzed for patients who administered at least one IP multiple dosing period. The following cases are excluded from the analysis for exposure.

- Patient discontinued after administration of single dosing will be excluded.
- If a patient could not follow up exact exposure duration of multiple dosing due to death, the patient will be excluded analysis for duration of therapy, cumulative dose and RDI.

In addition to the listing for study medication exposure, the listing for study medication accountability will be provided.

14.1. DERIVATIONS

- Duration of therapy (months) = (date of last study medication administration – date of first study medication administration + 1)/30.4375.
- Patient treated with some doses in cycle x will be counted as having received 'x cycles'. Patient will be counted to the maximum number of cycles received.
- RDI (%) = 100 * [Cumulative dose /(planned dose)], where cumulative dose is the actual cumulative dose delivered up to the earlier of progression (or a censoring event) by investigator or the actual last day of dosing and planned dose is the intended cumulative dose up to the earlier of progression (or a censoring event) by investigator or the actual last day of dosing.
- A dose interruption for a patient indicates a period in multiple dosing phase in which patient received no study treatment.
- A dose reduction for a patient indicates a period in multiple dosing phase in which patient's dose level is lower than the previous dose level.

15. EFFICACY OUTCOMES

Efficacy analyses will be performed based on the evaluable for response population. Sensitivity analysis will be performed to assess the robustness of the conclusions of the efficacy analysis.

15.1. PRIMARY ENDPOINTS

15.1.1. PARTS A, B (DOSE ESCALATION AND DOSE EXPANSION PHASES) AND PART D (OUTSIDE KOREA)

Parts A, B, and C

- Parts A and B: Safety and tolerability (Please refer to section 16)

Part D

- Part D: Safety and tolerability, and PK of YH25448

15.1.2. PART C (DOSE EXTENSION PHASE)

- Objective Response Rate (ORR)

ORR is defined as the percentage of patients who have at least one confirmed partial or complete response (PR or CR) prior to disease progression or recurrence in dose expansion and extension phases.

Patients who do not have a tumor response assessment for any reason will be considered non-responders and will be included in the denominator when calculating the response rate. Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR. ORR will be presented with two-sided 95% confidence intervals using Clopper-Pearson interval for part A and the normal approximation for part B by dose level and total.

15.2. SECONDARY EN DPOINTS

15.2.1. SECONDARY EFFICACY VARIABLES & DERIVATIONS

15.2.1.1. Tumor Shrinkage

Tumor size is defined as the sum of the lengths of the longest diameters of the target lesions (TL). If <1/3 of the target lesion measurements for any RECIST assessment are missing then the results will be scaled up mentioned in the section 7.5.

Percentage change in tumor size will be determined for patients with measurable disease at baseline and is derived at each visit by the percentage change in the sum of the diameters of TLs compared to baseline. Baseline for RECIST is defined to be the last evaluable assessment prior to starting treatment. For example, the percentage change from baseline in tumor size at 6 weeks = (Week 6 value – baseline value)/baseline value x 100.

The best change in tumour size (defined as the maximum reduction from baseline or the minimum increase from baseline, in the absence of a reduction) will include all assessments prior to progression or start of subsequent anti-cancer therapy. If it is known that the patient has died within 14 weeks (98 days) of start of treatment and has no evaluable RECIST assessments, best change will be imputed as 20%. However, if a large number of imputations are required, a sensitivity analysis may be performed without such imputation.

For brain metastatic patients, change in tumor size will also be reported separately for extracranial lesion and intracranial.

Change in tumor size at week 6

Whenever tumor size data for the week 6 visit is available then this will be used in the analysis. If ≤ 1/3 of the target lesion measurements at week 6 are missing then the results will be scaled up as mentioned in the section 7.5.

If, after applying the above considerations to the missing data, there is still missing tumor size measurement data (tsm data) at week 6, the imputation process outlined below will be applied:

(a) If there is no tsm data at week 6, but there is tsm data collected at a visit prior to week 6 or the first visit after week 6, use all of the available data up to and including the first visit after week 6 (i.e. baseline and all visits up to and including the first visit after week 6) to fit a linear regression to the individual patient's baseline and follow-up assessment(s) to generate an estimated value for tsm at week 6 and hence impute a change from baseline at week 6.

(b) If there is no tsm data at week 6 but there is evidence of progression for the individual, where evidence of progression is defined as progression of non-target lesions, the appearance of new lesions or as determined by an investigator, impute a change from baseline at week 6 as 20%. If the patient has an imputed value from a), use the maximum of 20% or the imputed value in the TSA.

(c) If there is no evidence of progression for the individual, use the imputed value calculated in a) if data available. If no data available, assume that the data is missing completely at random, the patient will be excluded from the analysis.

(d) If it is known that the patient has died, impute a change from baseline at week 6 as the maximum of 20% or the largest percentage increase calculated from actual or imputed

All imputed data will be derived within the reporting dataset with a corresponding flag against the imputed value to show that this value has been programmatically derived. The target and overall visit responses will be derived through programming.

The absolute values, change in target lesion tumour size from baseline and percentage change in target lesion tumour size from baseline will be summarised using descriptive statistics and presented at each timepoint and by dose group. Summaries and waterfall plots (bar charts) indicating percentage change from baseline in the sum of the diameters of target lesions at week 6 and week 12 will be produced if there are 3 patients with measurable disease at baseline. If there is only limited data then percentage change in tumor size will be listed only. In waterfall plots, shades of bars will indicate best objective response of the patient. Reference lines at the +20% and -30% change in tumor size levels will be added to the plots, which correspond to the definitions of progression and 'complete or partial' response respectively.

Best target lesion diameter change (%), which is defined as the lowest percentage change (best reduction percentage or smallest percentage increase) of sum of target lesion diameters among all post-baseline measurements, will be presented graphically with all patients regardless of their dosing level.

Listings of tumor assessments for target lesion, non-target lesion, and new lesion will be presented in a listing. In addition, a listing of overall response including lesion responses, sum of diameters and the corresponding change from baseline will be provided.

If a visit contains imputed data or discrepancy on programmed target or overall visit response, a listing will be provided including both derived and non-derived sum of diameters, the corresponding change from baseline, programmed or non-programmed target and overall visit responses.

15.2.1.2. Best Overall Response (BOR)

The BOR categories (CR, PR, SD [including non-CR/non-PD], PD, NE, Unknown) will be derived based upon time point tumor responses during the study as assessed by ICR as well as the investigator. BOR of SD must occur at least 5 weeks (6weeks minus the 7-day visit window) after the first dose of IP. If a patient has a BOR of non-CR/non-BOR will be grouped with the SD category.

A patient's overall best objective response will be determined:

- CR: At least one visit response of CR confirmed by repeat imaging at least 4 weeks later with

no evidence of progression between confirmation visits.

- PR: At least one visit response of PR confirmed by repeat imaging at least 4 weeks later with no evidence of progression between confirmation visits.
- SD: stable disease recorded at least 35 days after start of treatment (6 weeks from start of treatment, and also allowing a -7 day visit window). For example, an overall visit response of SD on day 28 will not be considered as SD ≥6weeks.
- PD: Progression, or death in the absence of CR/PR or SD.
- NE: No evidence of CR/PR or SD or PD or death.

For patients who progress and subsequently have a response, then the best objective response is only derived from assessments up to and including the time of the progression (i.e., it will not include the response after the patient has progressed).

Of note, output for intracranial overall response and intracranial diameters will be presented for BrM cohort.

Table 1. Visit Response (extracranial and intracranial disease)

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non CR/Non PD	No	PR
CR	NE	No	PR
PR	Non PD or NE	No	PR
SD	Non PD or NE	No	SD
NA	Non CR/Non PD	No	SD (Non CR/Non PD)
NE	Non PD or NE	No	NE
NA	NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Table 2. Overall Visit Response (extracranial and intracranial disease)

Extracranial lesion visit response	intracranial lesion visit response	Overall response
CR	CR	CR
CR	NA	CR
NA	CR	CR
CR	PR or SD	PR

Extracranial lesion visit response	intracranial lesion visit response	Overall response
CR	NE	PR
PR	CR/PR/SD or NE	PR
SD	CR/PR/SD or NE	SD
NA	PR/SD	SD
NE	Non PD or NE	NE
NA	NE	NE
PD	Any	PD
Any	PD	PD

15.2.1.3. Duration of Response (DoR)

DoR is defined as the time from the date of first documented responses that is subsequently confirmed until date of documented progression or death whichever comes first. The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. If the response is not confirmed, it will not be included.

If a patient does not progress following a response, then their duration of response will use the PFS censoring time.

For those patients with confirmed response, the date of response will be the date of first documented response, not the date of confirmatory tumor assessment for that response.

DoR in responding patients will be summarized using descriptive statistics and the number of responding patients with a duration of response (>3; >6; >9; >12 months) will be presented by dose group. A Kaplan-Meier plot and median DoR with 95% CI (calculated from the Kaplan-Meier plot) will be presented by dose level and total.

The time and duration of response per patient will also be displayed in a swimmer graph. For part A, the swimmer graph will also be sorted by T790M status.

15.2.1.4. Disease Control Rate (DCR)

DCR is defined as the proportion of patients with a best overall response (BOR) of CR, PR or SD for extracranial and intracranial. In the case of stable disease, assessments should have met the stable disease criteria for at least 5 weeks after the start of treatment. DCR will be presented with two-sided 95% confidence intervals using Clopper-Pearson interval for part A and the normal approximation for parts B, C and Part D by dose level and total. DCR will be presented together with ORR and BOR.

15.2.1.5. Progression Free Survival (PFS)

PFS is defined as the time from the first day of study treatment to the time of disease progression or death (by any cause in the absence of progression). If a patient has not experienced progressive disease or died before the end of study for any reason, progression-free survival will be censored at the day of the last adequate tumor assessment, which is not necessarily confirmed.

PFS (months) = (date of 1st PD or death or last evaluable RECIST assessment – reference start date+ 1) / 30.4375.

Start date of PFS:

- First day of study treatment

For event and censoring rules, please refer Table 3.

Table 3. Event/Censoring Rules

Situation	Data of Progression or Censoring	Outcome
No baseline tumor assessments	First administrated date	Censored
Progression documented between scheduled visits	Earliest of - Date of radiological assessment showing new lesion (if progression is based on new lesion); Or - Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions)	Event
No progression	Date of last radiological assessment of measured lesions	Censored
Treatment discontinuation for undocumented progression		
Treatment discontinuation for toxicity or other reason		
New anticancer treatment started		
Death before first PD assessment	Date of death	Event
Death between adequate assessment visit		
Death or progression after two or more missed assessments	Date of last radiological assessment of measured lesions	Censored

Note: PFS includes documented progression only

The analysis population for progression free survival will be the safety analysis population. PFS will be displayed using Kaplan-Meier plot. The number of events, median (calculated from the Kaplan-Meier plot), 95% Confidence interval and proportion of patients without an event at 6, 12, and 18 months will be summarized.

15.2.1.6. Overall Survival (OS)

OS is defined as the interval between the date of first dose and the date of patient death due to any cause. Patients who are lost to follow-up and patients who are alive at the date of data cut-off will be censored at the date the patient was last known alive.

The analysis population for overall survival will be the safety analysis population. OS will be summarized for the selected extension dose in expansion phase and extension phase.

The analyses for overall survival will resemble to those in PFS.

15.2.1.7. Objective Intracranial Response Rate (OIRR) (BrM patient)

OIRR is defined as the percentage of patients who have at least one confirmed partial or complete response (PR or CR) in intracranial lesion prior to disease progression or recurrence in brain metastatic patient.

The analysis for OIRR will be analogue to those in ORR. OIRR will be summarized for brain metastatic full analysis population and brain metastatic evaluable for response population.

OIRR will present together with Intracranial DCR (analogue to DCR) and Intracranial BOR.

15.2.1.8. Duration of Intracranial Response (DoIR) (Only BrM patient)

DoIR is defined as the time from the date of first documented responses (that is subsequently confirmed) in intracranial disease until date of documented progression or death whichever comes first. The time of the initial intracranial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR. If a patient does not progress following a response, then their duration of response will use the PFS censoring time.

The analysis for DoIR will be analogue to those in DoR. DoIR will be summarized for brain metastatic evaluable for response population.

15.2.1.9. Intracranial Progression Free Survival (IPFS) (Only BrM patient)

The analysis for IPFS will be analogue to those in PFS. IPFS will be summarized for brain metastatic full analysis population.

15.3. PATIENT REPORT OUTCOMES

- QLQ C-30
- QLQ LC-13
- QLQ BN-20 (BrM patient only)

The following PROs will be administered: European Organization for Research and Treatment of Cancer (EORTC) QLQ C-30 and QLQ LC-13.

The patient should complete the questionnaires at the scheduled clinic visit at baseline (screening) and then every 2 cycles. The patient should also complete a questionnaire at progression and their treatment discontinuation visit. If any scheduled PRO assessment is not completed the reason for non-completion should be recorded.

15.3.1. EORTC QLQ C-30

The EORTC QLQ C-30 consists of 30 items and measures cancer patients' functioning (HRQoL) and

symptoms (Aaronson NK et al 1993).

The following variables are to be calculated from the QLQ C-30 questionnaires:

- Global health status: Global health status
- Function scales: Physical functioning, Role functioning, Emotional functioning, Cognitive functioning, and Social functioning
- Symptoms: Fatigue, Nausea and vomiting and Pain
- Single items: Dyspnoea, Insomnia, Appetite loss, Constipation, Diarrhoea and Financial difficulties.

Each of these variables is described as a domain in the EORTC scoring manual. The Global health status, Functional scales and Symptom variables are multi-item domains [consist of more than one question.]. Each of the multi-item domains includes a different set of items - no item occurs in more than one domain. The single item domains consist of only one question. Figure 2 provides a description of which items contribute to which domains.

There are 28 questions whose options are: Not at all (score is 1), A little (score is 2), Quite a bit (score is 3), and Very much (score is 4). Question 29 and 30 are used for measuring global health status with scores ranged from 1 (very poor) to 7 (excellent).

The principle for scoring these scales is the same in all cases:

1. Estimate the average of the items that contribute to the scale; this is the raw score (RS).
2. Use a linear transformation to standardize the raw score, so that scores range from 0 to 100; a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms.

Technical summary

Suppose terms I1, I2… In are included in a scale, the procedure is as follows:

1. Calculate the raw score: Raw score = RS = (I1+ I2+…+In)/n
2. Apply the linear transformation to 0-100 to obtain the score S.

   Functional scales: S = {1 – ((RS – 1) /range)}*100

   Symptom scales/items: S = {(RS – 1) /range}*100

   Global health score /QoL: S = {(RS – 1) /range}*100

   Range is difference between the maximum possible value of RS and minimum possible value. The QLQ C–30 has been designed so that all items in any scale take the same range of values.

Example:

Emotional Functioning (EF) raw score = (Q21+ Q22+ Q23+ Q24)/4

EF score = {1 – ((RS – 1)/3)}*100

Missing items for QLQ C-30

If at least half of the items (i.e. 3 of 6 items, or 3 of 5 items) from the domain have been answered, we will use the available items to derive the domain score. As a result none of the single-item measures can be imputed.

Example:

Emotional Functioning if Q23 is missing (i.e. 3 items are not missing)

Raw score = (Q21+Q22+Q24)/3

EF Score = {1 – ((RS – 1)/3)}*100

Note that:

- A computed high score for a functional domain represents a high/healthy level of functioning, whereas a high raw score for a functional item represents a low/poor level of functioning;
- A computed/raw high score for the global health status/QoL represents a high QoL;
- But a computed/raw high score for a symptom domain/item represents a high level of symptomatology/problems.

Figure 2 The scoring approach for the QLQ C-30

	Scale	Number of items	Item range*	**Version 3.0** Item numbers	Function scales
Global health status / QoL					
Global health status/QoL (revised)†	QL2	2	6	29, 30	
Functional scales					
Physical functioning (revised)†	PF2	5	3	1 to 5	F
Role functioning (revised)†	RF2	2	3	6, 7	F
Emotional functioning	EF	4	3	21 to 24	F
Cognitive functioning	CF	2	3	20, 25	F
Social functioning	SF	2	3	26, 27	F
Symptom scales / items					
Fatigue	FA	3	3	10, 12, 18	
Nausea and vomiting	NV	2	3	14, 15	
Pain	PA	2	3	9, 19	
Dyspnoea	DY	1	3	8	
Insomnia	SL	1	3	11	
Appetite loss	AP	1	3	13	
Constipation	CO	1	3	16	
Diarrhoea	DI	1	3	17	
Financial difficulties	FI	1	3	28	

* *Item range* is the difference between the possible maximum and the minimum response to individual items: most items take values from 1 to 4, giving *range* = 3.
† (revised) scales are those that have been changed since version 1.0, and their short names are indicated in this manual by a suffix "2" – for example, PF2.

15.3.2. EORTC QLQ LC-13

The EORTC QLQ LC-13 is a complementary module measuring lung cancer-associated symptoms and side-effects from conventional chemotherapy and radiotherapy (Bergman B et al 1994). The QLQ LC-13 incorporates one multi-item domain to assess dyspnoea, and a series of single items assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and haemoptysis.

There are 43 questions whose options are: Not at all (score is 1), A little (score is 2), Quite a bit (score is 3) and Very much (score is 4).

A low score for a domain represents a high/healthy level.

Figure 3 describes the scoring approach for EORTC QLQ LC-13. As shown in the CSP, question numbers are preceded by 3 or 4, e.g., cough is Q31, and pain in chest is Q40.

Scoring procedure:

The scoring approach for the QLQ LC-13 is identical in principle to that for the symptom domains/single items of the QLQ C-30 (Section 15.3.1).

Imputation will be performed for QLQ LC-13 for Dyspnoea only if question 5 is not missing.

Example:

RS for dyspnoea will be Q3 + Q5 if Q4 is missing

RS for dyspnoea will be Q4 + Q5 if Q3 is missing

If Q5 is missing then dyspnoea will not be derived, however Q3 and Q4 will be summarized separately.

Figure 3 The scoring approach for the QLQ LC-13

Scale name	Scale	Number of items	Item range*	QLQ-LC13 Item numbers	†
Symptom scales / items					
Dyspnoea†	LCDY	3†	3	3,4,5	X
Coughing	LCCO	1	3	1	
Haemoptysis	LCHA	1	3	2	
Sore mouth	LCSM	1	3	6	
Dysphagia	LCDS	1	3	7	
Peripheral neuropathy	LCPN	1	3	8	
Alopecia	LCHR	1	3	9	
Pain in chest	LCPC	1	3	10	
Pain in arm or shoulder	LCPA	1	3	11	
Pain in other parts	LCPO	1	3	12	

* "Item range" is the difference between the possible maximum and the minimum response to individual items.

† The dyspnoea scale should only be used if all three items have been answered. Some respondents ignore question 5 because they never climb stairs; in this case, the score for the dyspnoea scale would be biased if it were based upon the other two items. Hence if item 5 is missing then items 3 and 4 should be used as single-item measures.

15.3.3. EORTC QLQ BN-20

The EORTC QLQ BN-20 is a complementary module measuring brain cancer-associated symptoms and side-effects from conventional chemotherapy and radiotherapy (Taphoorn MJ et al 2010). The QLQ BN-20 incorporates one multi-item domain to assess future uncertainty, visual disorder, motor dysfunction, and communication deficit, and a series of single items assessing headache, seizure, drowsiness, itchy skin, hair loss, weakness of legs and bladder control.

There are 20 questions whose options are: Not at all (score is 1), A little (score is 2), Quite a bit (score is 3) and Very much (score is 4).

A low score for a domain represents a high/healthy level.

Figure 4 describes the scoring approach for EORTC QLQ BN-20. As shown in the CSP, question numbers are preceded by 3 or 4, e.g., future uncertainty is Q31, and headache is Q34.

Scoring procedure:

The scoring approach for the QLQ BN-20 is identical in principle to that for the symptom domains/single items of the QLQ C-30 (Section 15.3.1).

Figure 4 The scoring approach for the QLQ BN-20

	Scale name	Number of items	Item range	QLQ-BN20 item numbers
Symptom scales / items				
Future uncertainty	BNFU	4	3	1, 2, 3, 5
Visual disorder	BNVD	3	3	6, 7, 8
Motor dysfunction	BNMD	3	3	10, 15, 19
Communication deficit	BNCD	3	3	11, 12, 13
Headaches	BNHA	1	3	4
Seizures	BNSE	1	3	9
Drowsiness	BNDR	1	3	14
Itchy skin	BNIS	1	3	17
Hair loss	BNHL	1	3	16
Weakness of legs	BNWL	1	3	18
Bladder control	BNBC	1	3	20

Remarks

- For the visual disorder scale, blurred vision (Q6) and double vision (Q7) can weaken each other's effect on the overall scale score as it is hard for patients to report their exact type of visual impairment. It is therefore acceptable to combine Q6 and Q7 into one response by taking its maximum and then combining into a 2 item visual disorder scale with Q8 should internal consistency be impaired.
- Due to the limited recall window (1 week), the seizure scale might underreport the actual seizure prevalence.

HRQoL compliance rates

Summary measures of overall compliance and compliance over time will be derived for EORTC QLQ C-30, LC-13 and BN-20 score. These will be based upon:

- Received forms = number of EORTC QLQ C-30 LC-13 and BN-20 forms received back
- Expected forms = number of patients still on treatment at the specified assessment time
- Evaluable forms = EORTC QLQ C-30, LC-13 and BN-20 forms with at least one domain that can be determined

Thus the overall compliance rate is defined as number of patients with an evaluable baseline and at least one evaluable follow-up form (as defined above), divided by the number of patients expected to have completed at least a baseline EORTC QLQ C-30, LC-13 and BN-20 form.

Compliance over time will be calculated separately for each visit, including baseline, as the number of patients with an evaluable form at the time point (as defined above), divided by number of patients still expected to complete forms. Similarly the evaluability rate over time will be calculated separately for each visit, including baseline, as the number of evaluable forms (per definition above), divided by the number of received forms. Compliance and evaluability rate over time will be provided in a data listing.

Domain scores for each questionnaire will be summarized using descriptive statistics (mean, STD, median, Q1, Q3, minimum, maximum, missing) of actual values and changes from baseline over time.

Listings will provide response for each item and domain score.

16. SAFETY OUTCOMES

All outputs for safety outcomes will be part C-1st line, part D and integrated analysis and based on the safety analysis population.

16.1. ADVERSE EVENTS

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. Relevant information is recorded on CRF page "Adverse Events".

Adverse Events (AEs) will be coded using latest available version of MedDRA to map verbatim adverse events to system organ class and preferred term. Severity of all AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0.

Any AE occurring before the first dose of investigational product (i.e., before study Day 1) will be included in the data listings but will not be included in the summary tables of adverse events. Treatment emergent adverse events (TEAEs) are defined as AEs that started on or after the first dose of study medication and prior to 28 day follow-up period (28+7 days after the last dose of study medication). Any adverse events in this period that occur after a patient has received further therapy for cancer (following discontinuation of investigational product) will be flagged in the data listings. AEs occurring after the 28 day follow-up period after discontinuation of investigational product will be listed separately, but not included in the summaries.

The summary of AEs table by dose level and overall will include the frequency (number and percentage) of patients with each of the following:

- TEAEs
- Drug Related TEAEs
- Serious TEAEs

- Drug Related Serious TEAEs
- TEAEs, Grade ≥3
- Drug Related TEAEs, Grade ≥3
- TEAEs leading to death
- Drug Related TEAEs leading to death
- TEAEs leading to dose reduction
- TEAEs leading to temporary drug interruption
- TEAEs leading to permanent drug withdrawal
- Other treatment-related TEAEs- overdose of study medication

Three listings will be provided for followings with relevant information:

- AEs occurred before the first dose of IP
- TEAEs
- AEs occurred after 28 day follow-up period

16.1.1. ALL TEAEs

The summary of incidence for following TEAEs will be provided:

- TEAE by PT with decreasing frequency
- TEAE by SOC/PT
- Drug Related TEAE by SOC/PT
- SAE by SOC/PT
- Drug Related SAE by SOC/PT
- TEAE with Grade >=3 by PT with decreasing frequency
- TEAE with Frequency >= 3% by PT with decreasing frequency and CTCAE Grade
- Drug Related TEAE with Frequency >= 3% by PT with decreasing frequency and CTCAE Grade
- TEAEs of special interest
- Drug Related TEAEs of special interest
- TEAEs of special interest, Grade ≥3
- Drug Related TEAEs of special interest, Grade ≥3

16.1.1.1. Severity

Severity is classed as CTCAE grade 1-5 (increasing severity). TEAEs starting after the first dose of study medication with a missing severity will be classified as severe (grade 3). If a patient reports a TEAE more than once within that SOC/ PT, the AE with the worst case severity will be used in the corresponding

severity summaries.

16.1.1.2. Relationship to Study Medication

Relationship, as indicated by the Investigator, is classed as Certain, Probable/Likely, Possible, Unlikely, Unassessable/Unclassifiable, and Not Related. Unless a relationship is classify as "Unlikely" and "Not related", its relationship to study medication will be classified as related. Missing relationship will be classified as related.

If a patient reports the same AE more than once within that SOC/ PT, the AE with the worst case relationship to study medication will be used in the corresponding relationship summaries.

16.1.2. SERIOUS ADVERSE EVENTS

Serious adverse events (SAEs) are those events recorded as "Serious" on the Adverse Events page of the CRF. A summary of serious TEAEs by SOC and PT will be prepared.

16.1.3. ADVERSE EVENTS LEADING TO FATAL

TEAEs leading to Death are those events which are recorded as "Fatal" on the Adverse Events page of the CRF.

16.1.4. DOSE LIMITING TOXICITY (DLT)

A detailed definition of DLT can be found in protocol section 4.1.3. Details will be captured on CRF page "DLT Summary" and "Adverse Event". Incidence rates of DLTs by SOC and PT will be summarized for DLT evaluable population.

All relevant information of DLT assessment including time between date of first study treatment and DLT event will be listed for DLT evaluable population.

16.2. DEATHS

Any patients die during the study conduct, as recorded on the "End of Study" CRF form, will be listed.

16.3. CLINICAL LABORATORY PARAMETERS

Laboratory samples will be analyzed at the study site's local laboratory. Laboratory assessments will include the following:

- Chemistry, which is recorded on CRF page "Chemistry"
- Hematology, which is recorded on CRF page "Hematology"
- Urinalysis, which is recorded on CRF page "Urinalysis"

Data recorded by the laboratory will be converted to the International System of Units (SI) and all

presentations will use SI units. Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of normal range (LLN), or "> X", i.e. above the upper limit of normal range (ULN), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

Quantitative laboratory measurements (Chemistry and Hematology) will be compared with the relevant laboratory reference ranges in SI units and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

For quantitative results, actual value of each scheduled visit, change from baseline for each post-baseline scheduled measurement, and normal range indicator will be presented by visit for safety analysis population.

Qualitative assessments (Urinalysis) will be summarized for all patients using the number of patients with results of negative, trace or positive.

16.3.1. LABORATORY NCI CTC AE GRADING

Quantitative laboratory measurements will be graded according to NCI CTC AE V4.03 wherever applicable. All grading will be based on lab values (being direct or some derived, corrected values) only, regardless of their interventional or symptomatic consequences. Grade 5 refers to fatal outcomes, which cannot be determined solely by lab values, therefore will not appear in the grading system. In addition to the usual defined categories, a further category denoted Grade 0 would include all other laboratory values except missing values. Missing results shall be graded as missing.

For some specific parameters with CTCAE grading in both high and low direction (e.g., calcium, glucose, magnesium, potassium, sodium), CTCAE in high and low directions will be presented separately, i.e. hyper for higher values of concern and hypo for lower values of concern. Appendix 2 displays the NCI CTC AE gradable parameters.

Shifts in toxicity grade from baseline to the worst toxicity grade will be provided for safety analysis population. In addition, shifts in toxicity grade from baseline to post baseline will be provided.

16.4. ELECTROCARDIOGRAM (ECG) EVALUATIONS

In addition to the overall evaluation, quantitative ECG will be in triplicate results and the average value will be used for analysis.

The following ECG parameters will be reported for this study:

- Heart Rate (beats/min)
- PR (msec)

- R-R (msec)
- QRS (msec)
- QT (msec)
- QTcF (msec)

The following summaries will be provided for ECG data:

- By visit summary for actual, change from baseline (Improved/ Unchanged/ Worsened/ Not Applicable/ Not compared) when applicable, and overall evaluation of ECG (Normal/ Abnormal, Not Clinically Significant (ANCS)/ Abnormal, Clinically Significant (ACS)/ Incomplete Analysis/ Uninterpretable/ Unable to Evaluate)
- Listing of patients with clinical significant change in post-baseline

All ECG results will be listed. In addition, a listing of AEs related to clinical changes in ECG post-baseline findings will be provided.

16.5. VITAL SIGNS

The following Vital Signs measurements will be reported for this study:

- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- Body Temperature (^0C)
- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse Rate (bpm)

The following summaries will be provided for vital signs data:

- Actual and change from baseline when applicable by visit

All vital signs results will be listed. In addition, a listing of AEs related to clinical changes in vital signs values will be provided.

16.6. PHYSICAL EXAMINATION

The following summaries will be provided for physical examination data:

- Incidence of clinical significant

All physical examination results will be listed.

16.7. OTHER SAFETY ASSESSMENTS

16.7.1. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

The Eastern Cooperative Oncology Group (ECOG) Performance Status will be summarized descriptively by visit from the "ECOG" CRF page. In addition, the proportion of categorized summary (0-1, 2-5) will be provided.

Details about ECOG performance status scores can be found in Section 6.2.2 of protocol.

A listing of ECOG Performance Status will be provided.

16.7.2. ECHOCARDIOGRAPHY

Echocardiography will be summarized descriptively by visit from "Cardiac Safety Monitoring" CRF page.

Actual value of echocardiography measured at each scheduled visit, change from baseline for each post-baseline scheduled measurement and New York Heart association classification will be presented by visit.

All echocardiography results including change from baseline for LVEF and relevant information will be listed.

17. PHARMACOKINETIC ANALYSES

Pharmacokinetic analyses will be performed based on the evaluable for pharmacokinetic analysis population. Pharmacokinetic analyses of the plasma and CSF concentration data for YH25448 and its metabolites will be performed by a Clinical PK Scientist at Yuhan.

The concentration data are used as supplied by the analytical laboratory for PK analyses. The units and decimal place of concentration and resulting PK parameters will be presented as they are received from the analytical laboratory.

17.1. CALCULATION OR DERIVATION OF PHARMACOKINETIC VARIABLES

For each patient, the following PK parameters will be calculated, whenever possible, based on the plasma concentrations of YH25448 and its potential metabolites including M7, according to the non-compartmental approach:

Following the single dose in parts A and D:

- YH25448 and its metabolites: Area under the plasma concentration-time curve from zero to the time of the last quantitative concentration (AUC_t), from zero to infinity (AUC_{inf}) and from zero to 24 hours (AUC_{0-24}), maximum plasma concentration (C_{max}), time to reach C_{max} (T_{max}), apparent

terminal elimination half-life ($t_{1/2}$), apparent terminal elimination rate constant (λ_z)

- YH25448: apparent plasma clearance (CL/F) and apparent volume of distribution (Vd/F)
- Metabolites: metabolic ratio (MR) of metabolites

Following the multiple doses in parts A, B and D:

- YH25448 and its metabolites: Area under the plasma concentration-time curve from zero to the end of the dosing interval (AUC_{ss}), maximum plasma concentration at steady state ($C_{max,ss}$), time to reach $C_{max,ss}$ ($T_{max,ss}$), accumulation ratio (R_{ac})
- YH25448: apparent plasma clearance at steady state (CL_{ss}/F)
- Metabolites: metabolic ratio at steady state (MR_{ss})

Following the multiple doses in parts A, B, C and D:

- YH25448 and its metabolites: Trough plasma concentrations on Days 1, 8, 15 of Cycle 1 (C_{D1}, C_{D8}, CD_{15})

Where possible the CSF concentration (C_{CSF}) value of YH25448 and its metabolites for each patient will be collected in parts A, B and C.

C_{max}, $C_{max,ss}$, T_{max}, $T_{max,ss}$, C_{D1}, C_{D8}, C_{D15} and C_{CSF} will be determined by visual inspection of the concentration-time profiles. AUC_t, AUC_{0-24} and AUC_{ss} will be calculated using the linear trapezoidal rule (Linear up/Log down). Where appropriate, AUC_{inf} will be extrapolated to infinity using the formula $AUC_{inf}=AUC_t+C_t/\lambda_z$ (where C_t is the last measurable concentration).

Where possible λ_z will be calculated by log-linear regression of the terminal phase of the concentration-time profiles where there are sufficient data, and $t_{1/2}$ will be calculated as $\ln 2/\lambda_z$. Following the single dose in parts A and D, if pre-dose concentration on Day 1, Cycle 1 (concentration before the start of first multiple dosing) is quantifiable, the concentration will be included in the calculation of λ_z. The regression with the largest adjusted-square of the correlation coefficient (adjusted R^2) will be selected to estimate λ_z, with these caveats:

- If the adjusted R^2 does not improve, but is within 0.0001 of the largest adjusted R^2 value, the regression with the largest number of points in used.
- λ_z must be positive, and calculated from at least three data points.

CL/F and CL_{ss}/F will be determined from ratio of dose/AUC_{inf} and dose/AUC_{ss}, respectively. Vd/F will be determined from the formula dose/(λ_z x AUC_{inf}). MR and MR_{ss} will be calculated as the ratio of the AUC_{inf} of metabolite/AUC_{inf} of YH25448 and the ratio of the AUC_{ss} of metabolite/AUC_{ss} of YH25448, respectively. R_{ac} will be calculated as the ratio of the AUC_{ss}/AUC_{0-24}.

Actual sampling times will be used in the PK parameter calculations. If the actual sampling times are missing, nominal times may be used. For any partial AUC determination, nominal time will generally be used for the end of the interval, and the actual times for partial AUC intervals may be used at the discretion of the Clinical PK Scientist.

For calculating the PK parameters, concentration values that are below the limit of quantitation (BLQ) will be set to zero, with defined exceptions as follows: any embedded BLQ value (between 2 quantifiable concentrations), BLQ values following the last quantifiable concentration in each PK evaluation period following single dosing on Day 1 Cycle 0 and multiple dosing on Day 1 Cycle 2 will be set to missing.

If there are late positive concentration values following 2 BLQ concentration values in the apparent terminal phase, these values will be evaluated. If these values are considered to be anomalous, they will be set to missing. Any patient who has an entire concentration-time profile as recorded BLQ, the patient will be excluded from the PK analyses.

17.2. PHARMACOKINETIC STATISTICAL METHODOLOGY

Descriptive statistics for PK will be analyzed by integrating Parts A, B, and C. PK summaries of Part D will be presented separately.

Plasma concentrations of YH25448 and its metabolites will be summarized by nominal sampling time. Plasma concentrations, CSF concentrations and PK parameters will be summarized according to dose by the following summary statistics: number of patients, arithmetic mean, standard deviation (STD), arithmetic coefficient of variation (CV%), median, minimum, maximum, geometric mean, and geometric CV%. Parameters following single and multiple dosing will be summarized separately.

In addition, in the integrated Parts A, B and D, plasma concentrations and PK parameters at 240 and 320 mg will be summarized in each group of Asian and non-Asian patients by dose, if the number of patients in the group is 5 or more. Dose-normalized PK parameters will also be summarized in each group of Asian and non-Asian patients.

In figures and descriptive statistics for plasma concentration data including trough plasma concentrations (C_{D1}, C_{D8}, C_{D15}), BLQ values will be treated as half of the lower limit of quantification (½LLOQ), with the exception of the value for 'not detected (ND)', which is set to zero. In Part D, descriptive statistics for trough plasma concentration data on Day 1 of every other cycle from Cycle 3 onwards will be analyzed at each nominal sampling time with at least 3 measured concentrations at each dose from the latest concentration data supplied by the analytical laboratory prior to database lock. If all the values are BLQ in all patients by each nominal sampling time or by each dose for trough plasma concentrations, then the arithmetic mean, arithmetic STD, median, minimum, maximum and geometric mean are presented as zero, and the arithmetic and geometric CV% are denoted as not applicable (NA).

In descriptive statistics for CSF concentration data, BLQ values will be set to ½LLOQ, with the exception of the ND value, which is set to zero. If all the values are BLQ in all patients by each dose, then the arithmetic mean, arithmetic STD, median, minimum, maximum and geometric mean are presented as zero, and the arithmetic and geometric CV% are denoted as NA.

In the integrated Parts A and B, the dose proportionality of YH25448 will be assessed using a power model with ln-transformed AUC_t, C_{max}, AUC_{ss}, $C_{max,ss}$ values as dependent variables and the ln-transformed dose as an independent variable:

$$\ln(\text{PK parameter}) = \alpha + (\beta \times \ln(\text{dose}))$$

$$\text{ie, PK parameter} = e^{\alpha} \times (\text{dose})^{\beta}$$

where α is the intercept, and β is the slope, measuring the extent of dose proportionality. Dose

proportionality implies that β=1 and will be assessed by estimating β along with its 90% confidence interval.

Ethnic comparison of PK profiles and parameters in patients outside Korea and Korean patients after administration of single dose and multiple dose of 240 and 320 mg will be conducted. Natural log-transformed primary parameters, C_{max}, and AUC_{last}, $C_{max,ss}$ and AUC_{ss} of YH25448, will be analyzed by analysis of variance, and point estimates and 90% confidence intervals of the geometric mean ratio (Test / Reference) will be calculated. 'Test' and 'Reference' are classified into four cases as shown in Table 4. In each case, the comparative analysis will be performed.

Table 4. A plan to evaluate the effect of ethnicity on PK in patients outside Korea (Part D) and Korean patients (Parts A and B)

Cases	Reference	Test
1. Using PK parameters at each dose	Korean patients in Parts A and B	Patients outside Korea in Part D
2. Using dose-normalized PK parameters	Korean patients in Parts A and B	Patients outside Korea in Part D
3. Using PK parameters at each dose	Asian patients in Parts A, B and D	Non-Asian patients in Parts A, B and D
4. Using dose-normalized PK parameters	Asian patients in Parts A, B and D	Non-Asian patients in Parts A, B and D

Additional analyses related to the PK profiles may be performed and will be reported outside of the CSR.

18. REFERENCES

YH25448-201_Clinical Protocol_Final_Eng Ver 9.0_08-Jan_2021
YH25448-201_Clinical_Protocol_Ver_11_final_20210108

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

Dates & Times

Depending on data available, dates and times will take the form DDMMMYYYY HH:MM:SS.

Spelling Format

English US

Listings

All listings will be ordered by the following (unless otherwise indicated in the template):

- Dose Level
- Subject ID
- Cycle or Date (where applicable)

APPENDIX 2. CTC AE GRADABLE PARAMETERS

Domain	Field ID	Field Name	PT using CTCAE (1)	PT using CTCAE (2)
Hematology	HGB	Hemoglobin	Anemia	Hemoglobin increased
	WBC	Leukocyte	White blood cell decreased	Leukocytosis
	NEUT	Neutrophils	Neutrophil count decreased	
	LYM	Lymphocytes	Lymphocyte count decreased	Lymphocyte count increased
	PLAT	Platelet Count	Platelet count decreased	
Chemistry	ALB	Albumin	Hypoalbuminemia	
	ALT	ALT	Alanine aminotransferase increased	
	AST	AST	Aspartate aminotransferase increased	
	ALP	Alkaline Phosphatase	Alkaline phosphatase increased	
	BILI	Total Bilirubin	Blood bilirubin increased	
	CA	Calcium	Hypercalcemia	Hypocalcemia
	CREAT	Total Creatinine	Creatinine increased	
	GLUC	Glucose	Hyperglycemia	Hypoglycemia
	MG	Magnesium	Hypermagnesemia	Hypomagnesemia
	K	Potassium	Hyperkalemia	Hypokalemia
	SODIUM	Sodium	Hypernatremia	Hyponatremia
	UREAN	Urea Nitrogen		
	TROPONI	Troponin I	Cardiac troponin I increased	
Urinalysis	UPRO	Protein	Proteinuria	
	URBC	URBC	Hemoglobinuria	
ECG	External Data	QTcF	Electrocardiogram QT corrected interval prolonged	

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