YUHAN

Clinical Protocol

YH25448-201
(Trial also known as: 73841937NSC2001)

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)

Protocol Version: Final Eng Ver 11.0
(Formerly referred to in the United States of America as YH25448-201/USA-1)

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EudraCT NUMBER: 2019-003106-28

SIGNATURE PAGE

SPONSOR SIGNATORY

YUHAN Corporation

Printed Name: PPD

Title: _____

Signature: _____

Date: 2021-11-12

Janssen Research & Development, LLC

Printed Name: PPD

Title: _____

Signature: _____

Date: _____

INVESTIGATOR SIGNATORY

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Printed Name: _____

Title: _____

Signature: _____

Date: _____

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Initial Eng ver.1.0	17-NOV-2016	Not Applicable
Protocol ver. 2.0	10-JAN-2017	Exclusion of Korean patients for Part C 1st line therapy cohort, applying the comments from MFDS, and others including word correction etc.
Protocol ver. 3.0	06-APR-2017	Change the inclusion criteria for Part A and clarification the meaning according to the change of KOR version 3.0.
Protocol ver. 4.0	11-DEC-2017	Change the Inclusion/Exclusion criteria, detailed description of analysis set and correct errors according to the change of KOR version 5.0.
Protocol ver. 5.0	04-MAY-2018	Deletion of Part C Dose Extension Phase Brain Metastasis (BrM) cohort, deletion of ”except Korea” and change in the patients’ number for Part C 1st line therapy cohort, and others according to the change of KOR version 6.0.
Protocol ver. 6.0	30-NOV-2018	Change the inclusion criteria for Part C 2nd line therapy cohort, detailed description of withdrawal consent procedure, clarification of SRC at Part B & Part C and others according to the change of KOR version 8.0.
Protocol ver. 6.0/USA-1	15-Apr-2019	Add study centers in United States and description of Part D: US patients, to enroll patients in the US, according to the change of KOR version 8.0(Eng version 6.0).
Protocol ver. 6.1/USA-1	21-May-2019	Add dose modification guideline of YH25448 for management of toxicity for Part D.
Protocol ver. 7.0	30-Jul-2019	Change the standard for causality assessment, time schedule for vital sign and ECG assessment for Part D, and reflect other changes to unify protocol for Korea and outside Korea. Sponsor name for Part D is changed from Yuhan to Janssen.

Protocol ver. 8.0	25-Feb-2020	Updated to allow collection of optional whole blood samples for pharmacogenetic analysis of GSTM1 in Part D (ex-Korea PK study), to clarify that central confirmation of TnI+ is not required in Part D (ex-Korea PK study), and to clarify that treatment will not be restarted after diagnosis of ILD, in line with Korean HA guidance.
Protocol ver. 9.0	08-Jan-2021	Application of changes in visit frequency and clinical trial procedure following changes in data collection after the primary data base lock.
Protocol ver. 10.0	13-Apr-2021	To re-insert safety assessments for Part D after primary DBL (19 Apr 2021) to allow protocol consistency across part D countries following a request from the MHRA.
Protocol ver. 11.0	19-Nov-2021	Removed requirement for long-term follow-up of patients in Part D.

Amendment Protocol Ver 11.0 (19 Nov 2021)

Overall Rationale for the Amendment: The requirement for long-term follow-up of patients in Part D was removed.

Section number and Name	Description of Change	Brief Rationale
6.1 Study Plan for Flow Chart/Time and Events Schedule Table 11. Part D: Patients Outside Korea	Added footnote 20 to indicate that, as of Protocol Amendment 11, follow-up visits will not be required for patients in Part D and overall survival and subsequent anticancer therapy data will not be collected. Updated footnote 17 to clarify that follow-up visits will not be required for patients in Part D as of Amendment 11.	Long-term follow-up is no longer required for patients in Part D.
6.2.6.4 Follow-up	Added a statement that, as of Protocol Amendment 11, follow-up visits will not be required for patients in Part D and overall survival and subsequent anticancer therapy data will not be collected.	Long-term follow-up is no longer required for patients in Part D

SYNOPSIS

Clinical Protocol
YH25448-201
(Trial also known as: 73841937NSC2001)

Title of Study: 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)

Study Sponsorship: Study Parts A, B, and C are sponsored by Yuhan Corporation under protocol identifier YH25448-201, and Study Part D is sponsored by Janssen Research & Development under protocol identifier 73841937NSC2001.

Estimated Number of Study Centers and Countries/Regions: Approximately 20 centers in Korea and approximately 10 centers outside Korea.

Study Phase: Phase I/II

Study Design: Multicenter, Open-label trial. There are four parts to this study. Part A, Dose escalation phase. Part B, Dose expansion phase. Part C, Dose extension phase. Part D, Safety, tolerability, efficacy and PK evaluation in patients enrolled outside Korea, including the United States of America (US). Note that Parts A through C are specific to Korean sites only and as of 26 Nov 2018, the safety tolerability, efficacy and PK of YH25448 have been evaluated in approximately 127 patients enrolled in Korea in dose escalation (Part A) and expansion phase (Part B) and 67 patients in dose extenstion phase at 240mg QD dose (Part C).

Primary Objective (Parts A, B, and C): To evaluate the safety, tolerability and efficacy of YH25448 when given orally to patients with EGFRm+ locally advanced or metastatic NSCLC.

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, DCR, tumor shrinkage and PFS using RECIST 1.1 as assessed by an independent central review of radiological information and overall survival (OS).

Primary and Secondary Objectives of Part D: Applies to patients enrolled outside of Korea only

Primary Objective:

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

Secondary Objectives:

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).

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).

Exploratory Objectives (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.

Overall Study Design (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.

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.

Part D: Overall Study Rationale and Design in patients outside Korea

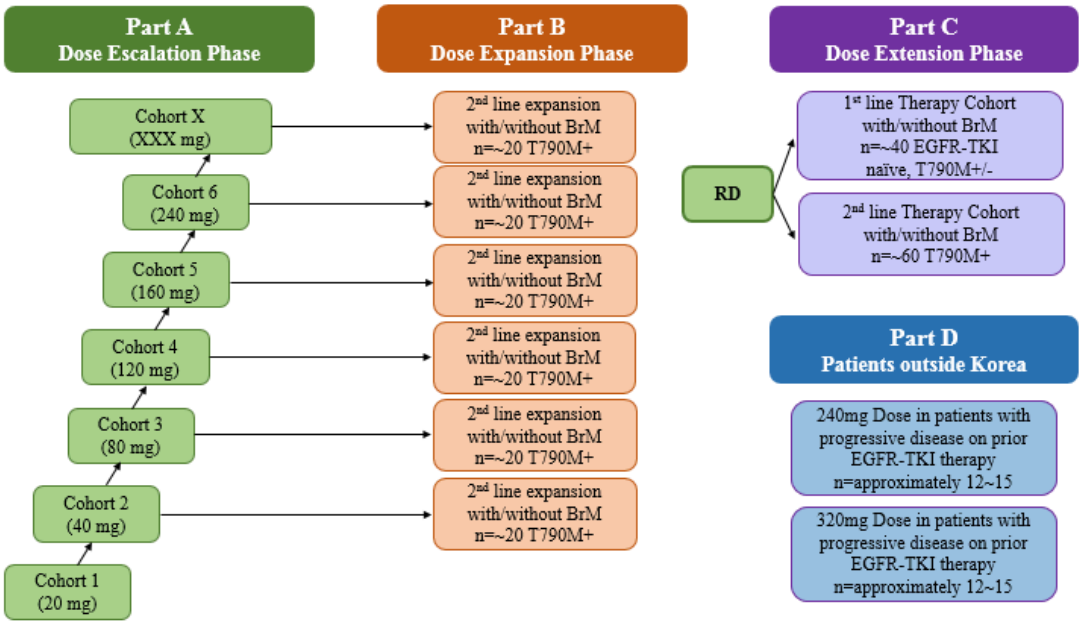
This is a phase I/II, open-label, multicenter study of YH25448 administered orally in patients with EGFRm+ NSCLC with or without asymptomatic brain metastasis. A PK study (Study YH25448-101), using the current RP2D of 240 mg in 12 Caucasian (3 Russian, 4 Turkish, 4 Moroccan, and 1 French) and 12 Korean healthy volunteers all enrolled from Korea, showed that the AUC_{last} and C_{max} were respectively 40% and 30% lower in Caucasian compared to Korean patients. Consequently, additional dose testing is required to support the RP2D in Caucasians outside Korea, including the US. Based on current PK data from this study (Study YH25448-201) of patients with EGFRm+ NSCLC, increasing the dose of YH25448 from 240 mg to 320 mg increases both the AUC_{ss} and $C_{max,ss}$ by about 20%. The 320 mg dose and has been shown to be safe in 5 Korean patients with no dose limiting toxicity (DLT). As of the data cutoff date of 26 Nov 2018, there were no treatment discontinutions due to adverse event at 320 mg cohort and the dose appears to be safe and tolerable. Comparing safety in the 320 mg (n 5) vs 240 mg (n 24) cohort, all grade adverse drug reactions (ADRs) were similar in both dose cohorts with pruritis, rash, decreased appetite and muscle spasms the most frequent. One patient

with ADR of Grade 3 pneumonitis was reported in the 240 mg dose cohort. No ADR with Grade ≥3 was reported in the 320 mg cohort. In conclusion: 1) no DLT was observed at the 240 and 320 mg dose and 2) the overall safety profile was similar between 240 and 320 mg dose.

In Part D, 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.

Study Design



RD : recommended dose
BrM : brain metastasis

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 experienced clinical benefit from EGFR TKIs followed by progression 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 to be evaluated for additional dose cohort according to the necessary of dose escalation or dose de-escalation.

For PK assessment of single and multiple doses, patients will receive a single dose on Day 1 Cycle 0 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 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.

Dosing for cohort 1 will begin at 20 mg once daily.

Dose escalation and de-escalation will follow the scheme below, according to the following logic:

- Dose limiting toxicity (DLT) will be assessed once the first three patients completed Cycle 1 (i.e. 21 days).
- If no DLT is observed in a cohort of 3-6 evaluable patients then dose escalation may occur (see Table 1). Dose increases will be permitted after the review of safety data from a minimum of 3 evaluable patients has been performed.
- If one patient experiences a DLT in a group of 3 or more evaluable patients then the cohort will be expanded to include 6 evaluable patients. If only one DLT is observed in the complete cohort of 6 evaluable patients then dose escalation may occur.
- If 2 or more patients experience a DLT in a group of at least 3 patients up to 6 patients, the dose will be considered not tolerated and recruitment to the cohort and dose escalation will cease. A lower dose or a lower intermediary dose (de-escalation, see Table 2) may be considered to better define the MTD.
- If 2 or more patients experience a DLT in a group of up to 6 patients at the starting dose of 20 mg then 10 mg would be investigated.
- Prior to achieving MTD, the maximum absorbable dose is achieved (i.e. when no increase in exposure with increasing dose is observed), the scheduling of dose escalation or dose de-escalation can be changed.
- Prior to a dose escalation or de-escalation decision, the Safety Review Committee (SRC) will review all available safety and PK data.
- Dose escalation will not exceed doubling of the dose in principle.

The provisional dose escalation and de-escalation scheme is described in Table 1 and 2, respectively. All dose levels beyond cohort 1 may change in light of emerging safety, tolerability and PK data.

Table 1. Provisional dose escalation scheme

Cohort	**Dose (mg)** (to be administered once daily)
1	20
2	40
3	80
4	120
5	160
X	xxx

Table 2. Dose de-escalation scheme

Dose at time of toxicity (mg) (to be administered once daily)	**Lower intermediary dose* (mg)** (to be administered once daily)
320	260
240	200
160	140
120	100
80	60
40	30
20	10

*** Lower intermediary dose: The middle dose between assigned dose level and lower dose level.**

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 progression disease prior to enrolling in the study regardless of whether BrM has occurred or not (See Figure 1).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. SRC will determine the change of dose level and decide to quit patients enrollment based on emerging data from expansion phases.

Part C: Dose Extension Phase

Once MTD or RD is reached for Part C as a result of the overall evaluation of the results of Part A and B and after the reflection of this result in the protocol or IB, additional 2 cohorts of 100 evaluable patients will be enrolled to assess the efficacy, safety and tolerability of YH25448. Trough 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 EFGR TKIs treatments and whose progression of the disease has been confirmed after 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 occurence will be enrolled to assess the efficacy and tolerability of YH25448.

Part D: Patients outside Korea

As of 26 Nov 2018, the safety tolerability, efficacy and PK of YH25448 have been evaluated in approximately 127 patients enrolled in Korea in dose escalation (Part A) and expansion phase (Part B) and 67 patients in dose extension phase at 240 mg QD dose (Part C). YH25448 was found to be well tolerated with no dose limiting toxicity up to a maximum of 320 mg per day. The recommendend Phase 2 dose, based on an assessment of safety, efficacy and PK, is 240 mg per day.

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. Although enrollment will not be based on race, it is expected that approximately 80% of patients will be Caucasian.

Patients outside Korea will be enrolled into the 240 mg and 320 mg Cohort on an alternating basis, Management of individual patient toxicity will be according to Section 5.4.1.3.

Main Inclusion Criteria

1) **For Parts A, B and C only:** Histologically or cytologically (i.e., pleural effusion, ascites cases) confirmed diagnosis of NSCLC patients with single activating EGFR mutations (L858R or Exon19Del or G719X or L861Q).

   A. **In Part D**: Patients outside Korea with histologically or cytologically (ie, using pleural effusion, ascites) confirmed NSCLC with previously diagnosed EGFRm+, and who have had progressive disease on prior EGFR-TKI therapy.

2) Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1 patients with no deterioration over the previous 2 weeks and a minimum life expectancy of 3 months.

3) Patients who have at least one measurable extracranial lesion, not previously irradiated and not chosen for biopsy during the study screening period or one measurable lesion that has passed 14 days or more after biopsy, that can be accurately measured at baseline as ≥ 10mm in the longest diameter (except lymph nodes which must have short axis ≥ 15mm) with computerized tomography (CT) or magnetic resonance imaging (MRI), are suitable for accurate repeated measurement.

4) **In Part A**, patients who had experienced clinical benefit from EGFR TKIs followed by systemic objective progression while on continuous treatment with the authorized EGFR

TKIs. Prior to enrolling in the study, patients must have central confirmation of T790M+/- mutation status from a sample taken after progression disease on the EGFR TKIs therapy.

5) **In Part B**, patients who have been treated with the authorized EGFR TKIs and must be confirmed progression disease prior to enrolling in the study. Patients must have central confirmation of T790M mutation positive(+) from a sample taken after progression disease on the therapy recently.

6) **In Part C-2nd line therapy cohort,** patients who have been treated with the authorized EGFR TKIs and must be confirmed progression disease prior to enrolling in the study. Patients must have T790M mutation positive(+) from a sample taken after progression disease on the recent therapy which is confirmed by local or central lab using the method approved by MFDS. However, if the T790M mutation is confirmed locally, the collected tumor sample must be submitted for central confirmation before the enrollment.

7) **In Part C-1st line therapy cohort**, patients must have not received any EGFR-TKIs prior to enrolling in the study, and EGFR mutation status must be confirmed as positive by a qualified institutional laboratory or a central laboratory.

Main Exclusion Criteria

1) Symtomatic spinal cord compression (if steroid treatment is not required within at least 2 weeks prior to the start of the study treatment then the patient may be enrolled)

2) Brain metastases with symptomatic and/or requiring emergency treatment (e.g. Steroid for at least 2 weeks prior to start of study treatment).

3) Intracranial hemorrhage with symptomatic and/or requiring treatment

4) CNS complications that require urgent neurosurgical intervention (e.g. resection or shunt placement).

5) Leptomeningeal metastasis prior to study treatment.

6) Past medical history of interstitial lung disease (ILD), drug-induced IDL, radiation pneumonitis which required steroid treatment, or any evidence of clinically active ILD.

7) EGFR TKIs administration to treat T790M resistance mutation (For Parts A, B, and C only).

8) Any cardiovascular disease as followed,

   a) History of symptomatic CHF or serious cardiac arrhythmia requiring treatment

   b) History of myocardial infarction or unstable angina within 6 months of the first dose

of study treatment

c) LVEF <50%

Efficacy Endpoints

Primary Endpoints (Parts A, B, and C)

- Safety and tolerability (primary for dose escalation and expansion phase)
- Objective response rate (ORR) (primary for dose extension, secondary for dose escalation and expansion phases)

Secondary Endpoints (Parts A, B, and C)

- PK parameters of YH25448 and its metabolites following a single oral dose and multiple oral doses.
- Duration of response (DoR), disease control rate (DCR), tumor shrinkage
- Progression free survival (PFS) (secondary for dose expansion and extension phases)
- Overall survival (OS) (secondary for the selected extension dose in expansion phase and extension phase)

  For the BrM patients only (secondary for dose expansion and extension phases): objective intracranial response rate (OIRR), duration of intracranial response (DoIR), intracranial progression free survival (IPFS)

Primary and Secondary Efficacy Endpoints for Part D

Primary Endpoints

- Safety, tolerability, and PK of YH25448

Secondary Endpoints

- PK profiles of potential YH25448 metabolites in plasma, including M7, following a single oral dose and at steady state.
- Overall response rate (ORR)
- Duration of response (DoR)
- Disease control rate (DCR)
- Tumor shrinkage

- Progression free survival (PFS)
- Overall survival (OS)

Exploratory Endpoints (Parts A, B, and C)

- Patient Reported Outcome: EORTC QLQ LC-13, QLQ C-30, QLQ BN-20 (BrM patients only)
- Metabolite identification
- Biomarker data
- Pharmacogenetics
- Diagnostic tumor samples

Exploratory Endpoints (Part D)

- Pharmacogenetic assessment of variants that encode GSTM1

Safety Variables

AEs, physical examination, clinical laboratory information, vital signs, ECOG performance status, ECG parameters, and concomitant medications/procedures

Statistical Analyses

The analyses of data will be based on different anaylsis population according to the purpose of the analyses. Analysis populations are described below:

- Safety analysis population: All patients who received at least one dose of investigational product (IP)
- Evaluable for response population: All patients in the safety analysis population who has a baseline RECIST 1.1 assessment whose tumor EGFR 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).
- Brain metastatic full analysis population: All patients in the evaluable for response population who have a measurable and/or unmeasurable intracranial lesion at baseline.
- 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.

- Pharmacokinetic analysis population: All patients who have at least one measurable concentration collected post-dose.

Primary Analyses

Parts A and B (Dose Escalation and Dose Expansion Phases) and Part D (Patients outside Korea)

Safety and tolerability will be assessed in terms of AEs, physical examination, laboratory data, vital signs and ECG assessments. All patients who receive at least one dose of YH25448 will be included in the assessment of the safety profile (safety analysis population). These safety measures will be listed and summarized descriptively in the safety analysis population, as appropriate.

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), according to RECIST 1.1 and appendix F prior to disease progression or recurrence.

The analysis population for ORR will be the evaluable for response population.

ORR will be presented with two-sided 95% confidence intervals using the normal approximation.

Analyses will be performed using both the assessments by independent central review (ICR) as well as by investigator, but the primary analysis for ORR will be based on ICR.

Secondary Analyses

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 (same as PFS event time) whichever comes first. The time of the initial 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.

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

Progression Free Survival (PFS)

PFS is defined as the time from first dosing date until documented disease progression or death from any cause whichever first based on ICR as well as investigator assessment using

RECIST 1.1 or appendix F. Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. In general, the PFS censoring rules and the definition of progression date follow the Food and Drug Administration (FDA) "Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007)".

PFS will be summarized based on the safety analysis population for the expansion and extension phases. PFS will be displayed using Kaplan-Meier plot. The number of events, median (calculated from the Kaplan-Meier plot), and proportion of patients without an event at 6, 12, and 18 months will be summarized.

Disease Control Rate (DCR)

DCR is defined as the proportion of patients with a best overall response (BOR), extracranial and intracranial response of CR, PR or SD.

Two-sided 95% confidence intervals DCR will be calculated using asymptotic normal approximation by dose level and total.

Tumor shrinkage

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 target lesions compared to baseline.

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

The analysis population for change in tumor size will be the evaluable for response population.

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.

Objective Intracranial Response Rate (OIRR)

OIRR is defined as the percentage of patients who have at least one confirmed PR or CR in intracranial lesion, according to RECIST 1.1 or appendix F prior to disease progression or recurrence in the brain metastatic patients.

The OIRR will be analyzed by the brain metastatic full analysis population and brain metastatic evaluable for response population.

OIRR will be presented with two-sided 95% confidence intervals (Clopper-Pearson interval) by dose level and total.

Duration of Intracranial Response (DoIR)

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 (same as intracranial PFS event time according to appendix F) whichever comes first in brain metastatic patients.

DoIR will be analyzed by brain metastatic evaluable for response population.

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

Intracranial Progression Free Survival (IPFS)
IPFS is defined as the time from first dosing date until documented disease progression or death from any cause whichever first based on ICR as well as investigator assessment using RECIST 1.1 or appendix F in brain metastatic patients. Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment.

IPFS will be analyzed by the brain metastatic full analysis population.

IPFS will be presented in the Kaplan-Meier plot. The number of events, median (calculated from the Kaplan-Meier plot), and proportion of patients without an event at 6, 12, and 18 months will be summarized.

Overall Survival (OS)
OS will be assessed based on the date of first dose and vital status at the time of data cutoff date. OS is defined as the interval between the date of first dose and the date of patient death due to any cause. The analysis population for OS will be the safety analysis population. OS will be summarized for the selected extension dose in expansion phase and extension phase. OS will be displayed using Kaplan Meier plots. The number of events, median (calculated from the Kaplan Meier plot), and proportion of patients without an event at 6, 12 and 18 months will be summarized. As appropriate, summaries of the number and percentage of patients who have died, are still in survival follow-up, are lost to follow-up and have withdrawn consent will be presented.

Pharmacokinetic Analyses
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. Parameters following single and multiple dosing will be summarized separately. 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.

Comparison of PK profiles and parameters for patients outside Korea and Korean patients after administration of single dose and multiple dose of 240 and 320 mg will be conducted. Log-transformed primary parameters for each dose, C_{max}, AUC_{last}, $C_{max,ss}$ and AUC_{ss}, will be analyzed by analysis of variance, and point estimates and 90% confidence intervals of the geometric mean ratio (patients outside Korea/Korean patients) will be calculated.

Sample Size Determination

Part A: Dose Escalation Phase

Approximately 30 patients with EGFRm+ NSCLC who had progressed following prior EGFR TKIs therapy will be enrolled in dose escalation phase. The total number of patients will depend upon the number of dose escalations necessary. At least 3 and up to 6 evaluable patients will be required for each dose cohort.

Part B: Dose Expansion Phase

Approximately 20 evaluable patients with T790M+ mutation NSCLC on the basis of central confirmed T790M mutation result regardless of brain metastasis (2nd line expansion with/without BrM) who had progressed following prior EGFR TKIs therapy will be enrolled per dose cohort.

Part C: Dose Extension Phase

2nd line therapy cohort

A total of 60 evaluable patients is required for the 2nd line therapy cohort in Part C. This sample size will provide 88% power to test a difference of 45% (not considered clinically compelling) versus 65% (ORR of minimal clinically meaningful) using a one-sided 0.025 alpha level.

1st line therapy cohort

A total of 40 evaluable patients is required for the 1st line therapy cohort in Part C. This sample size will provide 93% power to test a difference of 55% (not considered clinically compelling) versus 80% using a one-sided 0.025 alpha level.

Part D: Patients outside Korea

Approximately 12-15 patients outside Korea will be enrolled at each 240 mg and 320 mg dose level to provide a minimum of 6 Caucasian patients with evaluable PK. Although enrollment will not be based on race, it is expected that approximately 80% of patients will be Caucasian. All patients will have progressed following prior EGFR TKI therapy.

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1. INTRODUCTION and STUDY RATIONALE

1.1. Investigational Product Development Rationale

One-third of all cancer deaths worldwide are still caused by lung cancer and non-small-cell lung cancer (NSCLC) constitutes approximately 80% of lung cancer patients. Only minor portion of NSCLC patients can be cured by surgery and most of the patients are diagnosed with locally advanced or metastatic disease.[1] Treatment of advanced NSCLC is initially decided by molecular subtypes of the tumor and if the patients harbour epidermal growth factor receptor (EGFR) mutation, EGFR tyrosine kinase inhibitors (TKIs) are recommended as the first-line therapy and the patients are highly sensitive to those agents.[2] Most patients who initially respond to gefitinib and erlotinib eventually become resistant and experience progressive disease. T790M, the point mutation of the gatekeeper residue in EGFR tyrosine kinase domain accounts for about 50-60% of these cases of acquired resistance. This had lead to the development of third generation EGFR-TKIs targeting T790M mutation.[3] Approximately half of patients with NSCLC harboring EGFR mutations develop brain metastasis (BrM) within 3 years from diagnosis.[6] Currently-available EGFR TKIs show limited efficacy for the treatment of brain metastases probably due to limited blood brain barrier (BBB) penetration of current EGFR inhibitors.[4,5]

YH25448 is an oral, highly potent, mutant-selective and irreversible EGFR TKIs targets both the T790M mutation and activating EGFR mutations while sparing wild type-EGFR. YH25448 is expected to benefitial for the NSCLC patients with brain metastasis due to good BBB penetratration property as well as for the treatment of primary lung lesion and extracranial lesions. This study will be conducted to evaluate the safety, tolerability and efficacy of YH25448 in locally advanced or metastatic NSCLC patients with EGFR mutations.

1.2. Summary of pre-clinical studies

YH25448 selectively and irreversibly inhibited EGFR single and double mutant kinase activity with IC_{50} values of 2 nM for L858R/T790M against 76 nM for wild type-EGFR. In the cell proliferation assays, GI_{50} values were 6 nM, 5 nM, and 711 nM for H1975 cells (L858R/T790M), PC9 cells (del19) and H2073 cells (wild type), respectively. In primary cancer cells from patients harboring EGFR mutations, YH25448 showed more potent inhibition of cancer cell growth compared to osimertinib. YH25448 treatment at the once-daily doses of 0.3-10 mg/kg resulted in dose-dependent tumor regression in subcutaneous tumors in mice implanted with H1975 cells and most of the mice showed complete tumor regression at 10 mg/kg. In an intracranial tumor implantation model using H1975 cells in mice, YH25448 achieved more significant, complete tumor growth inhibition and longer overall survival compared to same doses of osimertinib at the dose range of 1-50 mg/kg and EDmax of YH25448 was 25 mg/kg.

Plasma half life of YH25448 was 5.9-6.8 hr and tumor to plasma $AUC_{0\ last}$ ratio was 3.0-5.1 in the tumor-bearing mice. YH25448 also showed excellent penetration of the BBB with brain to plasma AUC ratio of 4.0 and 0.8 in rats and mice after oral administration, respectively and achieving CSF concentrations exceeding the IC_{50} value for pEGFR inhibition. Overall, the strong in vitro potency and high selectivity of YH25448 for mutant EGFR translated into robust in vivo efficacy. These findings indicate that YH25448 will be able to address the unmet needs for EGFR mutant-positive patients with brain metastasis. YH25448 was rapidly absorbed after oral administration in mice, rats and dogs with Tmax was between 0.5 and 4.0 hr. The systemic exposure of YH25448 was generally dose proportional in dogs and less than dose proportional in rodents. Oral bioavailability was 33.7% to 79.8% dependent on the species and dose levels.

The volume of distribution following intravenous administration was ranged 2.9-17.2 L/kg in animals indicating extensive distribution into tissues. Plasma protein binding rate of YH25448 was 99.0 to 99.5% in animals and it was 99.1% in human. After oral administration of ^{14}C-YH25448 in rats, radioactivity was widely detected in tissues and highest radioactivity was observed in the uveal tract followed by stomach, small intestine, liver, Harderian gland, and lung.

In emerging in vitro metabolism studies, glutathione (GSH)-conjugation by GSTM1 was found to be the most abundant metabolic pathway. The relatively minor oxidative metabolism of lazertinib is mainly CYP3A4-mediated, although 2C9, 1A2, and 2A6 may also contribute. In an excretion study in rats, biliary excretion of metabolites was the major route of elimination of lazertinib following single oral administration of ^{14}C-lazertinib, with only a small fraction (< 5%) of the dose excreted in urine. In metabolite identification studies using hepatocytes, no human specific metabolite was detected and only a trace amount of two metabolites (M6 and M7) was identified in the human hepatocytes.

The key findings in the safety pharmacology studies were as following:

- YH25448 inhibited the function of the hERG channel with IC_{50} value of 5.3 μM using a manual patch clamp technique. In a tissue bath assay using isolated rabbit heart, no relevant electrocardiographic and electrophysiological changes were observed after exposure up to 30 μM of YH25448.
- There were no notable effects on the cardiovascular system in dogs following administration of single oral doses up to 20 mg/kg of YH25448.
- A single oral gavage dose of up to 100 mg/kg YH25448 administered to rats caused no general clinical effects or effect on assessed neurological parameters.
- A single oral administration of 100 mg/kg YH25448 in rats resulted in no biologically relevant effects on assessed respiratory parameters.

The key findings in the toxicity studies were as following:

- In both rat and dog toxicology studies almost all the observations and findings are consistent with consequences of the pharmacological inhibition of EGFR by YH25448 or sequelae secondary to primary effects. A wide range of organs and tissues containing epithelial cell lineages were affected with changes spanning mild epithelial atrophy through to degenerative erosions, inflammation and necrosis.

- In a 2-week dose range finding (DRF) study in rats, animals daily administered with 0, 50, 100, or 150 mg/kg/day of YH25448. Animals given 150 mg/kg/day were sacrificed early due to test article-related decreases in mean body weights and food consumption. In blood chemistry analysis, the most prominent effects were correlated with decreased food consumption (lower total protein and albumin), dehydration (higher urea nitrogen, higher inorganic phosphorus), and hepatocellular alterations (higher aspartate aminotransferase (AST) and alanine aminotransferase (ALT)). Evidence of possible mild inflammation (higher white blood cells, neutrophils, and monocytes) and lower red blood cell mass were also observed. Based on these findings, the dose levels of 100 mg/kg/day and 50 mg/kg/day were considered as the maximum-tolerated dose (MTD), and the no observed adverse effect level (NOAEL), respectively.

- In a 4-week oral repeat dose toxicity study in rats, animals were administered a dose level of 0, 25, 50, or 100/75 mg/kg/day YH25448 via oral route for 4 weeks followed by a 2-week recovery phase. Two YH25448-related deaths were noted in 100/75 mg/kg/day group. Test article-related clinical observations included an increased incidence of skin lesions along with a decrease in mean body weights and food consumption noted in animals administered 100/75 mg/kg/day. These findings showed evidence of reversibility during the recovery phase. In clinical pathology examination, higher urea nitrogen and creatinine in animals administered ≥50 mg/kg/day and higher AST and ALT in animals administered ≥25 mg/kg/day was correlated with microscopic findings of tubular dilatation and slight papillary necrosis and minimal single cell hepatocellular necrosis in animals administered 100/75 mg/kg/day which exhibited reversibility during the recovery phase. YH25448-related microscopic findings were observed in other tissues (eye, bone, bone marrow, duodenum, testis, skin, epididymis, ovary, uterus, vagina and mandibular lymph node) and the severity of these findings increased in a dose-dependent manner with no findings at 25 mg/kg/day. Some of these findings exhibited partial or complete reversibility during recovery phase. Therefore, the dose level of 100/75 mg/kg/day is considered severely toxic dose 10 (STD10) due to mortality observed at this dose, and 50 mg/kg/day as the MTD, and 25 mg/kg/day as the NOAEL.

- In a 2-week DRF toxicity study in dogs, animals administered with vehicle or YH25448 at the dose of 15, 30, or 50 mg/kg/day once daily for 2 weeks. Administration of 15 mg/kg for 14 days was well tolerated; dose levels of 30 and 50 mg/kg were not tolerated, and resulted in the early sacrifice on Day 7 of all animals administered 50 mg/kg and one female administered 30 mg/kg. Clinical observations, including red conjunctiva, squinted eyes, hypoactivity, and/or abdominal splinting, along with body weight loss and decreased food consumption, were noted. Clinical pathology effects were predominantly consistent with inflammatory response. These effects included mildly to moderately increased fibrinogen and globulin concentrations and mildly to moderately decreased albumin concentration and albumin:

globulin ratio, although these were considered not adverse. The NOAEL and MTD of YH25448 was considered as 15 mg/kg/day.

- In a 4-week repeated toxicity study in dogs, YH25448 was administered daily via oral gavage to animals for 4 weeks and assessed the reversibility after a 2-week recovery phase. Oral administration of 5, 10, or 20 mg/kg/day YH25448 to dogs for 28 days was tolerated in both males and females administered 5 or 10 mg/kg/day, and in females administered 20 mg/kg/day. However, 20 mg/kg/day was not tolerated in males because of marked body weight loss, decreased food consumption and the early sacrifice of one male. YH25448-related microscopic findings (degeneration/ necrosis of the myocardium and vessel, mixed cell inflammation, thrombus, and haemorrhage) present in the hearts of two males administered 20 mg/kg/day resulted in the early sacrifice of one of the males. Markedly increased cardiac troponin I concentration correlated microscopically with cardiac degeneration/necrosis in two high dose males. YH25448 related microscopic observations were also noted in the duodenum (blunting and fusion of villi), skin (epidermal atrophy), and kidney (inflammation of the pelvis) in 20 mg/kg /day group. Mixed cell inflammation and reduced luminal sperm in the epididymis, decreased secretion in prostate, and decreased lymphocytes in multiple lymphoid organs were present in animals administered ≥10 mg/kg/day. Epithelial atrophy in the cornea and esophagus, testicular tubular degeneration, bone marrow hypercellularity, and mononuclear cell infiltration in the liver were present in animals administered ≥5 mg/kg/day. Some of these findings exhibited partial reversibility during recovery phase. No abnormal ophthalmic observations were noted. Also, no YH25448-related changes in PR interval, QRS duration, QT interval, corrected QT (QTc) interval, RR interval, or heart rate were observed in all dose groups. The HNSTD of YH25448 was 10 mg/kg/day for males and 20 mg/kg/day for females.

- There were no findings to indicate the potential for genotoxicity when YH25448 was assessed in the in vitro Ames and chromosome aberration test and in the in vivo micronucleus study in rats up to 2,000 mg/kg/day.

- YH25448 was not considered phototoxic in the in vitro assay in 3T3 cells.

Further details for non-clinical study results are provided in the investigator brochure (IB) and the results from the non-clinical studies support progression into clinical trials in patients with advanced NSCLC including brain metastatic conditions.

1.3. Study Rationale

YH25448 is a mutant-selective irreversible EGFR TKIs targeting both T790M mutation and activating mutations while sparing EGFR mutation. In the preclinical studies, YH25448 showed excellent efficacy in brain metastases model with NSCLC cells carrying T790M mutation and high BBB penetration profiles. Therefore, with improved penetration of the BBB and equipotent activity against both T790M mutation and activating EGFR mutations, YH25448 has the potential to provide clinical benefit to patients with NSCLC with brain metastasis. Also, it is expected that YH25448 would show low toxicity such as rash and diarrhea due to its good selectivity against EGFR mutation.

This is a first time in patient study primarily designed to evaluate the safety, tolerability, and efficacy of YH25448 in patients with EGFR mutation positive (EGFRm+) advanced NSCLC with or without asymptomatic brain metastasis who progressed following prior therapy with an EGFR TKIs agent. This study is composed of 4 parts; part A is a dose escalation phase, part B is a dose expansion phase, part C is a dose extension phase and part D is for patients outside Korea. NOTE: Study Parts A, B, and C are sponsored by Yuhan Corporation under protocol identifier YH25448-201, and Study Part D is sponsored by Janssen Research & Development under protocol identifier 73841937NSC2001.

In dose escalation phase, YH25448 will be escalated to reach either a maximum tolerated or absorbable dose in patients as defined by dose-limiting toxicity in NSCLC patients who progressed following prior EGFR TKIs treatment to evaluate the safety and tolerability. In dose expansion phase, further safety, tolerability, PK and efficacy will be evaluated at each dose level(s) of dose escalation phase in NSCLC patients who progressed following prior EGFR TKIs treatment and harbouring confirmed T790M mutation. In dose extension phase, additional 2 cohorts (2^{nd} line therapy cohort and 1^{st} line therapy cohort) will be enrolled to further assess the efficacy, safety, tolerability, and PK of YH25448 at the MTD or recommended dose (RD) defined through dose escalation phase and dose expansion phase. Results of these studies will serve as the evidence for further clinical development.

This study will also characterize the metabolite(s) profile of YH25448 and determine PK of its metabolite(s) in biological samples if necessary. Also, exploratory correlation between biomarker profiles and pharmacokinetics/pharmacodynamics will be analyzed.

Part D: Overall Study Rationale and Design in Patients Outside Korea

This is a phase I/II, open-label, multicenter study of YH25448 administered orally in patients outside Korea with EGFRm+ NSCLC with or without asymptomatic brain metastasis. An ethnicity study (Study YH25448-101), using the current RP2D of 240 mg in 12 Caucasian (3 Russian, 4 Turkish, 4 Moroccan, and 1 French) and 12 Korean healthy volunteers all enrolled from Korea, showed that the AUC_{last} and C_{max} were respectively 40% and 30% lower in Caucasian compared to Korean subjects. Consequently, additional dose testing is required to support the RP2D in Caucasians outside Korea. Based on current PK data from this study (Study YH25448-201) of patients with EGFRm+ NSCLC, increasing the dose of YH25448 from 240 mg to 320 mg increases both the AUC_{ss} and $C_{max,ss}$ by about 20%. The 320 mg dose and has been shown to be safe in 5 Korean patients with no dose limiting toxicity (DLT). As of the data cutoff date of 26 Nov 2018, there were no treatment discontinutions due to AE at 320 mg cohort and the dose appears to be safe and tolerable. Comparing safety in the 320 mg (n 5) vs 240 mg (n 24) cohort, all grade adverse drug reactions (ADRs) were similar in both dose cohorts with pruritis, rash, decreased appetite and muscle spasms the most frequent. One patient with ADR of Grade 3 pneumonitis was reported in the 240 mg dose cohort. No ADR with Grade ≥ 3 was reported in the 320 mg cohort. In conclusion: 1) no DLT was observed at the 240 and 320 mg

dose and 2) the overall safety profile was similar between 240 and 320 mg dose.

In Part D, 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.

1.4. Overall Risk/Benefit Assessment

1.4.1. Potential benefits

Non-clinical data demonstrated that YH25448 exerts anti-proliferative and pro-apoptotic activity in tumor models harboring EGFR single activating or T790M double mutations. Therefore, YH25448 may have the potential to provide clinical benefit both in terms of increased efficacy and decreased EGFR wild type toxicity in patients with advanced EGFRm+ NSCLC who are either treatment-naïve or who have had disease progression after treatment with an EGFR TKIs agent (+/- additional chemotherapy) and are diagnosed with T790M+ NSCLC. In the first line treatment population, YH25448 may have the potential to delay the development of EGFR TKIs resistance via the T790M mechanism.

Results from Part A and Part B of the current study as of 26 November 2018 in 127 Korean patients with EGFRm+ NSCLC were determined by independent central review, and are presented in the table below.

Table 3. Summary of tumor response (Independent central review)

	All Patients	T790M+ Patients	T790M- Patients
Number of evaluable patients	127	108	19
ORR	54%	57%	37%
Median PFS (months)	9.5	9.7	5.4

1.4.2. Potential risks

Section 1.2 of this protocol summarizes potential risks based upon non-clinical toxicity studies with YH25448 in rats and dogs, and in vitro experiments, with further detailed information available in the IB.

The monitoring and management of the potential risks is discussed below:

Gastrointestinal tract effects
Patients with refractory nausea, vomiting and chronic gastrointestinal diseases are excluded from participating in this study. Investigators will also be advised to follow the dose interruption and reduction as detailed in Section 5.4.

Dermatological effects
No specific dermatological exclusion criteria are included in this study, however, patients with any unresolved adverse event from prior therapy greater than CTCAE Grade 1 will be excluded from participation. Dermatological treatment should be instituted for patients with any CTCAE grade skin reactions, considered by the investigator to be causally related to YH25448.Investigators will also be advised to follow the dose interruption and reduction as detailed in Section 5.4. Photographs may be performed to record any clinically significant findings. These photographs should be available for review by the Sponsor if necessary.

Ocular surface effects
Ophthalmic assessment, including slit lamp examination, fundoscopic examination, eye examination and other tests by investigator's judgement will be performed at screening and should be repeated if a patient experiences any visual symptoms (including blurring of vision), with additional tests if clinically indicated by per investigator's judgement. Any clinically significant findings, including those confirmed by the ophthalmologist must be reported as an AE. Photographs should be performed to record any clinically significant findings. These photographs should be available for review by the Sponsor if necessary.

Ophthalmology examination results should be collected in the eCRF. Any patient developing corneal ulceration will be permanently discontinued from study treatment and should be followed regularly until resolution of the event.

Patients who wear contact lenses will be advised to discontinue wearing lenses if they have any mild to moderate eye symptoms (CTCAE grade ≤2) while receiving treatment with YH25448 until at least one week after symptoms have resolved. If a patient has a recurrence of eye symptoms or experiences any severe (CTCAE grade ≥3) ocular events they should discontinue wearing their contact lenses until at least one week after treatment with YH25448 is permanently discontinued. To monitor the progress, patients must not use any eye drops or ointment for treatment of eye symptoms, unless agreed by a investigator, at any time during the study until 1 week after YH25448 has been permanently discontinued. Patient will be advised to consult the clinic promptly if they have any eye symptoms.

Cardiovascular effects
Patients who have unstable cardiac conditions and risk factors for QT prolongations will be excluded from participation in this study. Concomitant use of regular medications that may prolong the QT interval will be restricted whenever feasible (See appendix G), but patients may receive any medication that is clinically indicated for the treatment of AEs. Electrolyte and vital sign assessments, including pulse rate and blood pressure, will be monitored regularly

throughout the study. A series of triplicate digital ECG assessments will be performed over a 24 hour period before/after the first single dose of YH25448, over a 24 hour after 22-day multiple dosing (Day 1 Cycle 2) and at the time of presumed steady state (Day 8 and Day 15 Cycle 1), with single ECGs being recorded at the beginning of each subsequent treatment cycle, as described in Section 6.2.4. The investigator or designated physician will review each ECG prior to discharge from the clinic and may refer to a local cardiologist if appropriate for immediate management of the patient. A paper copy should be filed in the patient's medical records. All digital ECG data will be transferred electronically for central analysis of heart rate, PR, R-R and QT intervals by an external cardiologist. If an abnormal ECG finding at screening or baseline is considered to be clinically significant by the investigator, it should be reported as a concurrent condition.

Echocardiography (or Multiple Gated Acquisition Scan (MUGA)) and troponin I (TnI) test will be performed regularly throughout the study until the–primary database lock and with the process described in detail in appendix B.

Respiratory effects
Patients with a past medical history of interstitial lung disease, drug-induced interstitial lung disease, radiation pneumonitis which required steroid treatment, or any evidence of clinically active interstitial lung disease will be excluded from participation in this study. If new or worsening pulmonary symptoms (eg, dyspnoea) or radiological abnormality suggestive of interstitial lung disease is observed, an interruption in study treatment dosing is recommended, and the Sponsor study team should be informed. Investigators should perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of interstitial lung disease should be considered and study treatment permanently discontinued.

In the absence of a diagnosis of interstitial lung disease study treatment may be restarted following consultation with the Sponsor Study Physician.

Liver effects
Patients with any evidence of severe or uncontrolled systemic liver disease, including those with known hepatitis B, hepatitis C, abnormal liver enzymes (defined as AST or ALT >2.5 x upper limit of normal (ULN), total bilirubin >1.5 x ULN if no evidence of liver metastases; AST or ALT >5 x ULN, total bilirubin >3 x ULN in the presence of liver metastases) at screening are excluded from participating in the study. During the study, liver function tests will be monitored regularly during the study and recorded at discontinuation. For Parts A, B and C: After the primary database lock, Liver function tests will be performed as clinically indicated per investigator discretion. The process described in detail in appendix A.

For Part D: After the primary database lock, please refer to the Schedule of Activities.

Hematopoietic effects

Patients with inadequate bone marrow reserve as demonstrated by any of the following laboratory values (absolute neutrophil count < 1.5 x 10^9/L; platelet count < 100 x 10^9/L; haemoglobin <90 g/L) will be excluded from the study. Hematological parameters will be monitored during the study and at permanent discontinuation. For Parts A, B and C: After the primary database lock, hematology will be performed as clinically indicated per investigator discretion.

For Part D: After the primary database lock, please refer to the Schedule of Activities.

Renal Effects

Patients with abnormal renal function as defined by creatinine >1.5 x upper limit of normal (ULN) concurrent with creatinine clearance < 50 mL/min at screening are excluded from participating in the study. During the study, kidney function tests (serum creatinine and blood urea nitrogen) will be monitored regularly during the study and recorded at discontinuation. As one case of suspected unexpected serious adverse reaction which is acute renal failure was reported during the study, this will be closely monitored. For Parts A, B and C: After the primary database lock, kidney function tests will be performed as clinically indicated per investigator discretion.

For Part D: After the primary database lock, please refer to the Schedule of Activities.

Reproductive organ effects

No reproductive toxicology or teratogenicity studies have been conducted with YH25448 to date, although the male and female reproductive tracts have been assessed as part of the 1 month toxicology studies. Therefore women of child bearing potential and all men will be required to use adequate contraceptive measures during the study and for an appropriate period thereafter. Women of child bearing potential must have a negative pregnancy test prior to first dose of study treatment. Women who are breast feeding will be excluded from participating in the study. Male patients will be advised to arrange for the freezing of sperm samples prior to the start of the study should they wish to father children, and not to donate sperm until 3 months after discontinuation of study treatment.

Possible drug-drug interactions

In *In vitro* studies, the major biotransformation pathway of YH25448 is CYP3A4-mediated metabolism. Hence, all patients must avoid concomitant use of medications, herbal supplements and/or ingestions of foods with known potent inducer or inhibitory effects on CYP3A4 activity whenever feasible. Such drugs must have been discontinued for an appropriate period before they administer the first dose of study treatment and for a period of 1 week after the last dose of YH25448. *In vitro* studies have shown that, YH25448 is an inhibitor of P-glycoprotein (P-gp), MRP4 and Breast Cancer Resistance Protein (BCRP). Therefore, medications, herbal supplements and/or ingestions of foods with known potent substrate of P-gp, MRP4 or BCRP

recommended to be avoided whenever feasible. Guidance on medications to avoid, medications that require close monitoring and on washout periods is given in appendix G. If medically feasible, patients taking regular medication, with the exception of inhibitors or inducers of CYP3A4 should be maintained on them throughout the study period. Patients may receive any medication listed **in** appendix G that is clinically indicated for treatment of adverse events.

Part D: Potential Risk Evaluation

As of 26 Nov 2018, the safety tolerability, efficacy and PK of YH25448 have been evaluated in approximately 127 patients enrolled in Korea in dose escalation (Part A) and expansion phases (Part B) and 67 patients in the dose extension phase at 240 mg QD (Part C). YH25448 was found to be well tolerated with no dose limiting toxicity up to a maximum of 320 mg per day. For a review of safety please see the Investigator's Brochure. The recommended Phase 2 dose, based on an assessment of safety, efficacy and PK, is 240 mg per day.

Based on current PK data from this study (Study YH25448-201) of patients with EGFRm+ NSCLC, increasing the dose of YH25448 from 240 mg to 320 mg increases both the AUC_{ss} and $C_{max,ss}$ by about 20%. The 320 mg dose and has been shown to be safe in 5 Korean patients with no dose limiting toxicity (DLT). As of the data cutoff date of 26 Nov 2018, there were no treatment discontinutions due to AE at 320 mg cohort and the dose appears to be safe and tolerable. Comparing safety in the 320 mg (n 5) vs 240 mg (n 24) cohort, all grade adverse drug reactions (ADRs) were similar in both dose cohorts with pruritis, rash, decreased appetite and muscle spasms the most frequent. One patient with ADR of Grade 3 pneumonitis was reported in the 240 mg dose cohort. No ADR with Grade ≥3 was reported in the 320 mg cohort. In conclusion: 1) no DLT was observed at the 240 and 320 mg dose and 2) the overall safety profile was similar between 240 and 320 mg dose. Therefore, based on the safety and tolerability observed in Korean patients, as well as the lower systemic exposure observed in Caucasian subjects, it is predicted that dosing Caucasian patients with YH25448 at 240mg and 320 mg (Part D) will have an acceptable benefit/risk profile.

1.4.3. Overall benefit-risk and ethical assessment

Non-clinical data of YH25448 support the notion that it will provide clinical benefit to the NSCLC patients with either activating EGFR mutations or T790M mutation. Especially, YH25448 is expected to can satisfy unmet medical needs for the treatment of NSCLC with brain metastasis. The non-clinical safety profile has not identified any risks that would preclude investigation in this setting. An overall evaluation of the nonclinical data indicates an acceptable risk/benefit profile for YH25448 to be further investigated in this study.

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 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 of radiological information and overall survival (OS).

2.3. Primary and Secondary Objectives of Part D: Applies to patients enrolled outside Korea

Primary Objective:

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

Secondary Objectives:

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 ORR, DoR, DCR, tumor shrinkage and PFS using RECIST 1.1 as assessed by investigator review of radiological information and OS.

2.4. 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 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. ETHICAL CONSIDERATIONS

3.1. Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH) and relevant local regulations

The study is to be conducted in compliance with the protocol. The protocol and any amendments and the Patient informed consent must receive Institutional Review Board (IRB) approval prior to initiation of the study.

All potential serious violations must be reported to the Sponsor immediately. A serious violation is a violation of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the patients of the study or the scientific value of the study.

Study personnel involved in the conduct of this study must be qualified by education, training, and experience for the appropriate performance of their respective task(s).

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g. loss of medical licensure, debarment).

Systems with procedures that assure the quality of every aspects of the study will be implemented.

3.2. Institutional Review Board/Ethics Committee

Prior to study initiation, the investigator must obtain written and dated approval from the IRB/EC for the protocol, consent form, Patient recruitment materials/process (e.g. advertisements), and any other written information to be provided to patients. The investigator or Sponsor should also provide the IRB/EC with a copy of the IB, as well as updates and other information (e.g. expedited safety reports, amendments, and administrative letters) in accordance with regulatory requirements or institution procedures.

3.3. Informed Consent

Investigators must ensure that patients or in situations where consent cannot be given by patients, their legally acceptable representatives are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate. Freely given written informed consent must be obtained from every patient (or in situations where consent cannot be given by patients, their legally acceptable representative) prior to clinical study participation, including informed consent for any screening procedures conducted to establish patient eligibility for the study. And investigators ensure that each patient is notified that they are free to withdraw from the study at any time and ensure a copy of each signed Informed Consent Form is given to the patient.

The rights, safety, and well-being of the study patients are the most important considerations and should prevail over interests of science and society.

4. INVESTIGATIONAL PLAN

4.1. Study Design and Rationale

4.1.1. Rationale for dose regimen, dose escalation scheme

The predicted efficacious dose range (20-160 mg) for the dose escalation phase (Part A) of the first-in-human study is based on the nonclinical PK and repeat-dose toxicology studies in several animal species as well as the mouse efficacy study data in conjunction with in vitro inhibition of ≥50% pEGFR signals in H1975 (L858R/T790M) cell lines; at which equivalent exposure in mice, tumor regression was achieved in xenograft tumors both subcutaneously and in the brain.

The international guidance for starting dose selection for agents in cancer patients (ICH S9)[7] recommends that the starting dose should be either 1/10th of the severely toxic dose (STD10) in rodent toxicity studies or 1/6th of the highest non-severely toxic dose (HNSTD) observed in non-rodent studies. Based on the findings in non-clinical GLP tox studies, in which dogs are defined as the most sensitive species, 10 mg/kg/day (HNSTD for male dogs) has been used in the calculation for human dose prediction. In rats, the STD_{10} was 100/75 mg/kg/day from the 1-month study. Using the conversion factors published on the FDA website[8] (FDA Guidance 2005), the maximum recommended starting dose (MRSD) derived from 1/10th of the rat STD_{10} was calculated to be 72 mg/day, whilst the MRSD derived from 1/6th of the dog HNSTD in male was calculated to be 53 mg/day. As a result of using the most conservative data, a starting dose of 53 mg/day is proposed for this study. Biologically active dose (BAD) which was defined as dose exhibits 90% tumor growth regression in the NSCLC H1975 intracranial tumor models in mice was 8.8 mg/kg/day for YH25448. This corresponds to human equivalent dose (HED) of 42.8 mg in adults. Therefore, the 20 mg starting dose is anticipated biologically active and covers pEGFR IC_{50} of H1975 cells for 24 hours. The proposed highest dose of 160 mg is twofold lower than maximum tolerated dose determined in 4-week toxicity study in dogs as the most sensitive species. The dose escalation scheme will not exceed doubling of the dose, in principle. However, up to a quadrupling of the dose may be permitted in the first two escalations only, if the drug concentrations from the first or second dose level are not measurable or are below the predicted target drug exposure for biological effect. This will ensure that the fewest possible cohorts are exposed to YH25448 below the presumed therapeutic dose. Non-clinical modeling provides only an approximate prediction of human PK, therefore the planned dose escalation scheme has the flexibility to be amended in light of emerging data.

As this is the first administration of YH25448 in humans, in the first cohort the administration of the first dose is separated by at least 7 days for the first 2 patients. This will ensure that any acute toxic effects of the administration will have sufficient time to be identified before additional patients are exposed. Once the completion of dosing of Cycle 1 in the last required

evaluable patient from one cohort, the start of dosing in the subsequent cohort in order for the SRC meeting to be called, and minutes of the dose escalation decisions to be distributed to all participating centers.

Part D: Overall Study Rationale and Design in Patients Outside Korea

This is a phase I/II, open-label, multicenter study of YH25448 administered orally in patients outside of Korea with EGFRm+ NSCLC with or without asymptomatic brain metastasis. An ethnicity study (Study YH25448-101), using the current RP2D of 240 mg in 12 Caucasian (3 Russian, 4 Turkish, 4 Moroccan, and 1 French) and 12 Korean healthy volunteers all enrolled from Korea, showed that the AUC_{last} and C_{max} were respectively 40% and 30% lower in Caucasian compared to Korean patients. Consequently, additional dose testing is required to support the RP2D in Caucasians outside Korea. Based on current PK data from this study (Study YH25448-201) of patients with EGFRm+ NSCLC, increasing the dose of YH25448 from 240 mg to 320 mg increases both the AUC_{ss} and $C_{max,ss}$ by about 20%. The 320 mg dose and has been shown to be safe in 5 Korean patients with no dose limiting toxicity (DLT). As of the data cutoff date of 26 Nov 2018, there were no treatment discontinutions due to AE at 320 mg cohort and the dose appears to be safe and tolerable. Comparing safety in the 320 mg (n 5) vs 240 mg (n 24) cohort, all grade adverse drug reactions (ADRs) were similar in both dose cohorts with pruritis, rash, decreased appetite and muscle spasms the most frequent. One patient with ADR of Grade 3 pneumonitis was reported in the 240 mg dose cohort. No ADR with Grade ≥3 was reported in the 320 mg cohort. In conclusion: 1) no DLT was observed at the 240 and 320 mg dose and 2) the overall safety profile was similar between 240 and 320 mg dose.

In Part D, patients outside Korea, including Caucasians, will be dosed with the current RP2D of 240 mg and 320 mg in order to test safety, tolerability, efficacy (including tumor response) and PK in patients outside of Korea.

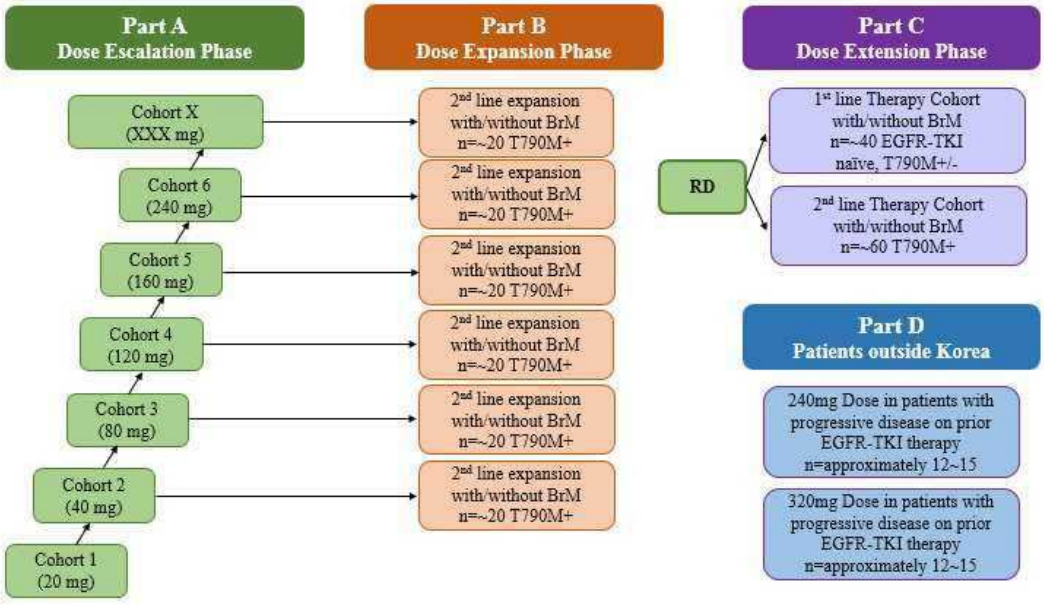
4.1.2. Study Design

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.

There are four parts to this study. Part A, Dose escalation phase, Part B, Dose expansion phase, and Part C, Dose extension phase, and Part D, patients outside 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.

Figure 1. Study Design



RD : recommended dose
BrM : brain metastasis

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 experienced clinical benefit from EGFR TKIs followed by progression disease while on continuous treatment with the authorized EGFR TKIs prior to enrolling in the study.

For the evaluating of DLT, at least 3 and up to 6 patients will be required for each cohort. It is possible to evaluate for additional dose cohort according to the necessity of dose escalation or dose de-escalation.

For PK assessment of single and multiple doses, patients will receive a single dose on Day 1 Cycle 0 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 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.

Dosing for cohort 1 will begin at 20 mg once daily.

Dose escalation and de-escalation will follow the scheme below, according to the following logic:

- Dose limiting toxicity (DLT) will be assessed once the first three patients completed Cycle 1 (i.e. 21 days).
- If no DLT is observed in a cohort of 3-6 evaluable patients then dose escalation may occur (see Table 4). Dose increases will be permitted after the review of safety data from a minimum of 3 evaluable patients has been performed.
- If one patient experiences a DLT in a group of 3 or more evaluable patients then the cohort will be expanded to include 6 evaluable patients. If only one DLT is observed in the complete cohort of 6 evaluable patients then dose escalation may occur.
- If 2 or more patients experience a DLT in a group of at least 3 patients up to 6 patients, the dose will be considered not tolerated and recruitment to the cohort and dose escalation will cease. A lower dose or a lower intermediary dose (de-escalation, see Table 5) may be considered in order to better define the MTD.
- If 2 or more patients experience a DLT in a group of up to 6 patients at the starting dose of 20 mg then 10 mg would be investigated.
- Prior to achieving MTD, the maximum absorbable dose is achieved (i.e. when no increase in exposure with increasing dose is observed), the scheduling of dose escalation or dose de-escalation can be changed.
- Prior to a dose escalation or de-escalation decision, the Safety Review Committee (SRC) will review all available safety and PK data.
- Dose escalation will not exceed doubling of the dose in principle.

The provisional dose escalation and de-escalation scheme is described in Table 4 and 5, respectively. All dose levels beyond cohort 1 may change in light of emerging safety, tolerability and PK data.

Table 4. Provisional dose escalation scheme

Cohort	**Dose (mg)** (to be administered once daily)
1	20
2	40
3	80
4	120
5	160
X	Xxx

Table 5. Dose de-escalation scheme

Dose at time of toxicity (mg) (to be administered once daily)	**Lower intermediary dose* (mg)** (to be administered once daily)
320	260
240	200
160	140
120	100
80	60
40	30
20	10

*** Lower intermediary dose: The middle dose between assigned dose level and lower dose level.**

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+ who have experience in the authorized EGFR TKIs therapy followed by progression disease prior to enrolling in the study regardless of whether BrM has occurred or not (See Figure 1).

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. SRC will determine the change of dose level and decide to stop patients enrollment based on emerging data from expansion phases.

Part C: Dose Extension Phase

Once the MTD or RD is determined for Part C as a result of the overall evaluation of the results of Part A and B and after reflection of this result in the protocol or IB, additional 2 cohorts of 100 evaluable patients will be enrolled to assess the efficacy, safety and tolerability of YH25448. Trough 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 whose progression of the disease has been confirmed after recent treatment regardless of BrM occurence.

2) **1st line therapy Cohort**

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

Part D: Patients Outside Korea

As of 26 Nov 2018, the safety tolerability, efficacy and PK of YH25448 have been evaluated in approximately 127 patients enrolled in Korea in dose escalation and expansion phases. YH25448 was found to be well tolerated with no dose limiting toxicity up to a maximum of 320 mg per day. The recommended Phase 2 dose, based on an assessment of safety, efficacy and PK, is 240 mg per day.

The goal of Part D is to test the safety, tolerability, efficacy and PK of YH25448 at the 240 mg and 320 mg dose levels in patients enrolled outside Korea. Approximately 12-15patients will be enrolled at each dose level to provide a minimum of 6 Caucasian patients with evaluable PK. Although enrollment will not be based on race, it is expected that approximately 80% of patients will be Caucasian.

Patients outside Korea will be enrolled into the 240 mg and 320 mg Cohort on an alternating basis, Management of individual patient toxicity will be according to Section 5.4.1.3.

4.1.3. Definition of dose-limiting toxicity

A DLT is defined as an adverse event or abnormal laboratory value that occurs from the first dose of study treatment (Day1, Cycle 0) up to the last dose of Cycle 1 (21 days from the start of multiple dosing) assessed as unrelated to disease progression, intercurrent illness, or concomitant medications that despite optimal therapeutic intervention meets any of the following criteria:

1) Hematological toxicity that is:
   - ≥ CTCAE grade 4 present for more than 4 days.
   - Febrile neutropenia.
2) Non-hematological toxicity ≥ CTCAE grade 3 including:
   - QTc prolongation (>500msec or 60msec above baseline).
3) Any other toxicity that :
   - Is greater than that at baseline, is clinically significant and/or unacceptable, and is judged to be a DLT by the SRC.
   - Is a protocol defined in toxicity management, see Section 5.4 (e.g. confirmed corneal ulceration).

- Result in a disruption of dosing schedule more than 14 days.

A DLT excludes:

1) Alopecia of any grade.

2) Isolated laboratory changes of any grade without clinical sequelae or clinical significance.

The incidence and type of DLT-type toxicity from Cycle 2 and beyond will be taken into account by SRC in determining dose escalation and de-escalation.

4.1.4. Definition of maximum tolerated dose

A dose will be considered non-tolerated and dose escalation will cease if 2 or more of up to 6 evaluable patients experience a DLT at a dose level. Once the non-tolerated dose is defined the MTD will be confirmed at the lower dose or the lower intermediary dose level below the non-tolerated dose may be investigated. Six evaluable patients are required to determine the MTD.

4.1.5. Definition of evaluable patients for DLT

For decision of dose escalation, an evaluable patient is defined as a patient that has received YH25448 and either:

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

4.1.6. Duration of therapy

Patients should continue on treatment with YH25448 until RECIST 1.1 defined progression or until treatment discontinuation criteria is met. There is no maximum duration of treatment as patients may continue to receive YH25448 beyond RECIST 1.1 defined progression as long as they are continuing to show clinical benefit, as judged by the investigator.

However, tumor assessment will not be performed if patients continuously take YH25448 without dose escalation after progression. If patients continue to receive the study drug after intracranial lesion has shown clinical benefit regardless of progression for extracranial lesion, tumor assessment will be continued every 2 cycles until progression for intracranial lesion is confirmed. 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 will be no intra-patient dose escalation for each cohort, but if the dose escalation is

required for the patients as judged by the investigator in the dose escalation and expansion phase, the dose escalation must be determined by both the Sponsor Study Physician and the investigator in advance. Tumor assessment can be performed until progression is confirmed after dose escalation.

Dose increase is available only if disease is progressing after showing clinical benefit and the escalated dose will be permitted within the range which is determined after the review of safety and toxicity data. If YH25448 is discontinued for reasons other than disease progression, the patient must continue RECIST 1.1 assessments every 2 cycles until disease progression or further lines of anticancer therapy are administered (with exception of Part A) 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.

4.2. Study Population

Each patient must meet all of the inclusion criteria and none of the exclusion criteria for this study at the time of starting study treatment. Under no circumstances can there be exceptions to this rule.

4.2.1. Inclusion Criteria

For inclusion in the study, patients must fulfill all of the following criteria.

1. Signed Written Informed Consent

1) Provision of signed and dated, written informed consent prior to any study specific procedures, sampling and analyses. For inclusion in optional genetic and/or biomarker research, patients must provide informed consent for the research.

2. Age and Sex

1) At least 20 years of age and older or adult men and women for each country.

2) Females should agree to use adequate contraceptive measure (as defined in Section 4.2.3), should not be breast feeding and must have a negative pregnancy test prior to start of dosing if of child-bearing potential or must have evidence of non-child-bearing potential by fulfilling one of following criteria at screening:

Post-menopausal defined as aged more than 50 years and ameorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments.

Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation.

Women under 50 years old would be considered postmenopausal if they have been

ameorrhoeic for at least 12 months following cessation of exogenous hormonal treatment, and have serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels in postmenopausal range for the institution.

3) Male patients who have not undergone a vasectomy must agree to use barrier contraception i.e. condoms, and refrain from donating sperm until 3 months after last drug is taken.

4) During the study, and for 3 months after receiving the last dose of study drug, female patients must agree not to donate eggs (ova, oocytes) and male patients must agree not to donate sperm for the purposes of assisted reproduction.

3. Target disease

1) **Parts A, B and C only**: Histologically or cytologically(i.e., pleural effusion, ascites cases) confirmed diagnosis of NSCLC with single activating EGFR mutations (L858R or Exon19Del or G719X or L861Q). EGFR mutation status should have been determined using well-validated and robust methodology which has been approved by the regulatory authority. In the country where diagnosis of EGFR mutation does not need to use regularity approved kit, well-validated methodology will be used.

   A. **In Part D**: Patients outside Korea with histologically or cytologically (ie, using pleural effusion, ascites) confirmed NSCLC with previously diagnosed EGFRm+, and who have had progressive disease on prior EGFR-TKI therapy.

2) Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1 with no deterioration over the previous 2 weeks and a minimum life expectancy of 3 months.

3) Patients who have at least one measurable extracranial lesion, not previously irradiated and not chosen for biopsy during the study screening period or one measurable lesion that has passed 14 days or more after biopsy, that can be accurately measured at baseline as ≥ 10mm in the longest diameter (except lymph nodes which must have short axis ≥ 15mm) with computerized tomography (CT) or magnetic resonance imaging (MRI), are suitable for accurate repeated measurement.

4) **In Part A**, patients who had experienced clinical benefit from EGFR TKIs followed by systemic objective progression while on continuous treatment with the authorized EGFR TKIs. Prior to enrolling in the study, patients must have central confirmation of T790M+/- mutation status from a sample taken after progression disease on the EGFR-TKIs therapy.

5) **In Part B**, patients who have been treated with the authorized EGFR TKIs and must be confirmed progression disease prior to enrolling in the study. Patients must have central confirmation of T790M+ mutation from a sample taken after progression disease on the therapy recently.

6) **In Part C-1st line therapy cohort**, patients must have not received any EGFR-TKIs prior to enrolling in the study, and EGFR mutation status must be confirmed as positive by a qualified institutional laboratory or a central laboratory.

7) **In Part C-2nd line therapy cohort,** patients who have been treated with the authorized EGFR TKIs and must be confirmed progression disease prior to enrolling in the study. Patients must have T790M mutation positive(+) from a sample taken after progression disease on the recent therapy which is confirmed by local or central lab using the method approved by MFDS. However, if the T790M mutation is confirmed locally, the collected tumor sample must be submitted for central confirmation before the enrollment.

4.2.2. Exclusion Criteria

Patients must not enter the study if any of the following exclusion criteria are fulfilled.

1. Intervention with any the following:

1) An unapproved investigational product from another clinical study within 30 days of the first dose of study treatment.

2) Treatment with an EGFR TKIs (e.g. erlotinib or gefitinib) within 8 days or approximately 5x half-life, whichever is the longer, of the first dose of study treatment or other investigational products within approved indication of marketed product (if sufficient wash-out time has not occurred due to schedule or PK properties, an alternative appropriate wash-out time based on known duration of time to reversibility of drug related adverse events could be agreed upon by the Sponsor and the Investigator).

3) Any cytotoxic chemotherapy or other anticancer drugs for the treatment of advanced NSCLC from a previous treatment regimen within 14 days of the first dose of study treatment.

4) Major surgery (excluding for vascular access) within 4 weeks of the first dose of study treatment, or have an anticipated need for major surgery during the study.

5) Radiotherapy with a wide field of radiation within 4 weeks or radiotherapy with a limited field of radiation for palliation within 1 week of the first dose of study treatment with the exception of patients receiving radiation to more than 30% of the bone marrow which must be completed within 4 weeks of the first dose of study treatment.

6) Patients currently receiving (or unable to stop use at least 1 week prior to receiving the first dose of YH25448) medications or herbal supplements known to be inhibitors or inducers of CYP3A4.

7) Any unresolved toxicities from prior therapy, greater than Common Terminology Criteria

for Adverse Events (CTCAE) grade 1 at the time of starting 1st study treatment with the exception of alopecia.

8) EGFR TKIs administration to treat T790M resistance mutant (For Parts A, B and C only).

2. Medical History and Concurrent Disease

1) Symptomatic spinal cord compression (if steroid treatment is not required within at least 2 weeks prior to the start of the study treatment then the patient may be enrolled).

2) Brain metastases with symptomatic and/or requiring emergency treatment (e.g. Steroid for at least 2 weeks prior to start of study treatment).

3) Intracranial hemorrhage with symptomatic and/or requiring treatment

4) CNS complications that require urgent neurosurgical intervention (e.g. resection or shunt placement).

5) Leptomeningeal metastasis prior to study treatment.

6) Past medical history of interstitial lung disease (ILD), drug-induced IDL, radiation pneumonitis which required steroid treatment, or any evidence of clinically active ILD.

7) Carcinoma besides NSCLC requiring treatment or any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which in the investigator's opinion makes it undesirable for the patient to participate in trial or which would jeopardise compliance with the protocol. Screening for chronic condition is not required.

8) Any cardiovascular disease as followed,

   a) History of symptomatic CHF or serious cardiac arrhythmia requiring treatment

   b) History of myocardial infarction or unstable angina within 6 months of the first dose of study treatment

   c) LVEF <50%

9) Active hepatitis with HbsAg+ or anti-HCV Ab+, confirmed positive HIV test results.

10) Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of study medication.

11) History of hypersensitivity to active or inactive excipients of YH25448 or drugs with a similar chemical structure or class to YH25448.

12) Clinically significant chronic infection or significant medical or psychiatric illness.

13) Judgment by investigators that the patient should not participate in the study if the patient is unlikely to comply with study procedure, restrictions and requirements.

14) In addition, the following are considered criterion for exclusion from the exploratory genetic research: Previous allogeneic bone marrow transplant, Non-leukocyte depleted whole blood transfusion within 120 days of the date of the genetic sample collection.

3. Cardiac and Clinical Laboratory Criteria

1) Any of following cardiac criteria:
   a) Mean resting corrected QT interval (QTc) > 470 msec obtained from 3 electrocardiograms (ECGs), using the screening ECG machine derived QTc value
   b) Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG eg, complete left bundle branch block, third degree heart block, second degree heart block, PR interval >250msec
   c) Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age in first degree relatives or administration of concomitant medication known to prolong the QT interval

2) Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values;
   a) Absolute neutrophil count (ANC) < 1.5 x 10^9/L
   b) Platelet count < 100 x 10^9/L
   c) Hemoglobin <90g/L
   d) Alanine aminotransferase (ALT) >2.5 times the upper limit of normal (UNL) if no demonstrable liver metastases or 5 times ULN in presence of liver metastases
   e) Aspartate aminotransferase (AST) >2.5 times the UNL if no demonstrable liver metastases or 5 times ULN in presence of liver metastases
   f) Total bilirubin >1.5 times ULN. If no liver metastases or >3 times ULN in the presence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia) or liver metastasis
   g) Serum creatinine >1.5 times ULN concurrent with creatinine clearance <50ml/min measured by center's standard method (e.g. Cockcroft and Gault equation). Confirmation of creatinine clearance is only required when creatinine is >1.5 times ULN
   h) Unexplained inadequate liver function except ALP elevation which investigator can

not determine on bone metastases

i) In case of Troponin I test result finally confirmed by central lab exceeded ULN (TnI+). In Part D, central laboratroy confirmation of TnI+ is not required.

4.2.3. Restrictions

The following restrictions apply while the patient is receiving study treatment and for the specified times before and after:

1) Female patients of child-bearing potential should use reliable methods of contraception from the time of screening until 3 months after discontinuing study treatment. Acceptable methods of contraception include total and true sexual abstinence, tubal ligation, hormonal contraceptives that are not prone to drug-drug interactions [IUS Levonorgestrel Intra Uterine System (Mirena), Medroxyprogesterone injections (Depo-Provera)], copper-banded intra-uterine devices and vasectomised partner. All hormonal methods of contraception should be used in combination with the use of a condom by their male sexual partner for intercourse.

2) Female patients should not breast-feed during the trial and for at least 2 months after the last dose of study treatment.

3) Male patients should be asked to use barrier contraceptives (i.e., by use of condoms) during sex with all partners during the trial and for a washout period of 3 months. Patients should avoid procreation for 3 months after completion of trial treatment. Patients should refrain from donating sperm from the start of dosing until 3 months after discontinuing study treatment. If male patients wish to father children they should be advised to arrange for freezing of sperm samples prior to the start of study treatment.

4) Patients who wear contact lenses must discontinue wearing their lenses if they have any mild to moderate eye symptoms (CTCAE grade ≤2) while receiving treatment with YH25448 until at least one week after symptoms have resolved. If a patient has a recurrence of eye symptoms or experiences any severe (CTCAE grade ≥3) ocular events such as corneal ulcer, they must discontinue the administration of YH25448 permanently. To monitor the progress, patients must not use any eye drops or ointment for treatment of eye symptoms, unless agreed by a investigator, at any time during the study until 1 week after YH25448 has been permanently discontinued. Patient should consult the clinic promptly if they have any concerns.

4.2.3.1. Concomitant treatments

Guidance on medicines to avoid, medications that require close monitoring and on washout periods based on potential interactions with YH25448 are provided in appendix G.

Other anticancer agents, investigational agents and radiotherapy should not be given while the

patient receiving study treatment. The patient may be allowed to take localized palliative radiotherapy if it has been confirmed that there is no disease progression on the local lesion excluding target lesion. Study drug interruption is not required in the case of local palliative radiotherapy for pain control, but for local palliative radiotherapy to chest, study drug should be interrupted during and up to 7 days post the palliative radiotherapy.

Blood transfusions are allowed at any time during the study.

Granulocyte colony stimulating factors should not be used prophylactically during Cycle 1. Use of prophylactic colony stimulating factors may be considered after Cycle 1 following discussion with the Sponsor Study Physician.

Patients may receive treatment with corticosteroids and/or bisphosphonates for the treatment of bone metastases.

Other medication, other than those described above, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF. After the primary database lock, only concomitant medications related to SAEs will be collected.

4.2.3.2. Prohibited Treatments

In *In vitro* studies, the major biotransformation pathway of YH25448 is CYP3A4-mediated metabolism. Hence, all patients must prohibit concomitant use of medications, herbal supplements and/or ingestion of foods with known potent inducer/inhibitory effects on CYP3A4. Such drugs must have been discontinued for an appropriate period before they administer the first dose of study treatment and for a period of 1 week after the last dose of YH25448. *In vitro* studies have shown that, YH25448 is an inhibitor of P-gp, MRP4 and Breast Cancer Resistance Protein (BCRP). Therefore, medications, herbal supplements and/or ingestion of foods with known potent substrate of P-gp, MRP4 or BCRP are recommended to be avoided whenever feasible. Guidance on medicines to avoid, medications that require close monitoring and on washout periods is to be provided in appendix G. Except inhibitor or inducer of CYP3A4, appropriate regular concomitant medication should be maintained during the study period. Patients may receive any medication listed in appendix G that is clinically indicated for treatment of adverse events.

4.2.4. Discontinuation of Investigational Product and withdrawal from Study

Patients may be discontinued from investigational product in the following situations:

- Patient decision. The patient is at any time free to withdraw his/her participation in the study, without prejudice

- Adverse events
- Severe non-compliance to this protocol as judged by the investigator and/or Sponsor
- Disease progression as per RECIST 1.1, in the opinion of the investigator, the patient is no longer receiving clinical benefit.
- Patients incorrectly initiated on investigational product (Section 4.2.4.2)
- Pregnancy
- Termination of the study by the Sponsor

4.2.4.1. Procedures for discontinuation of a patient from investigational product

Once the study treatment is permanently discontinued, then it cannot be restarted.

The investigator should complete a discontinuation visit eCRF upon a patient's discontinuation of study treatment or withdrawal from the study, see Section 4.2.4.3.

Any AEs and SAEs occurring in any patient who discontinues study treatment for reasons other than disease progression should be collected until 28 days of last dosing. Also, unless consent is withdrawn, tumor assessment should be performed as scheduled in the protocol (see Table 8, Table 9, Table 10 and Table 11) until disease progression or subsequent anti-cancer therapy. Study procedure related SAEs and anti-cancer treatment must be captured until the patient no longer has tumor assessments (disease progression or permanent withdrawal from the study).

After the primary database lock, there may be some patients remaining on study treatment. For these patients who are continuing to receive YH25448, Sponsor will collect information during the treatment period and for 28(+7) days after last dose on SAEs, deaths (including those due to disease progression), discontinuation due to AEs/SAEs and drug accountability.

4.2.4.2. Procedures for handling patients incorrectly initiated on investigational product

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Where patients that do not meet the inclusion criteria are enrolled in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post initiation, the investigator should inform the Sponsor Study Physician immediately. The decision on when to discontinue the ineligible patient from the study is based on the medical/safety risk for the patient. The Sponsor Study Physician is to ensure all such contacts are appropriately documented.

4.2.4.3. Procedure for withdrawal from study

Patients are at any time free to withdraw from the study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen by an investigator and undergo the assessments and procedures scheduled for the post study assessment. For Parts A, B and C only: A separate consent form for study withdrawal will be provided to obtain withdrawal consent from the patients, and then the procedure will be followed as option chosen from the withdrawal consent form. (see Section 6.2.6). Adverse events should be followed up (see Sections 7.3) and the patient should return study drug.

5. TREATMENTS

5.1. Study Treatment

Patients will receive relevant dose level of YH25448 as assigned group orally QD for 21 days in 21-day Cycles until documented evidence of disease progression, unacceptable toxicity, noncompliance, or withdrawal of consent, or the investigator decides to discontinue treatment, whichever comes first. Doses should be taken approximately 24 hours apart at the same time point each day before eating meal under fasting. Alternative frequencies (e.g. bid) or intermittent schedules may be investigated in response to emerging safety, tolerability or PK data. If a patient misses taking a scheduled dose, within a window of 12 hours, it is acceptable to take the dose. If it is more than 12 hours after the dose time, the missed dose should not be taken, and patients should be instructed to take the next dose at the next scheduled time. If a patient vomits after taking their YH25448, they should not make up for this dose, but should take the next scheduled dose.On the days when blood samples will be collected for PK analysis, the scheduled dose should be taken at the investigational center after the pre-dose PK sample has been collected. Patients should fast from midnight on the day before the study visit. If the Patient vomits the dose, it should not be replaced but the time of vomiting should be captured in source document. PK blood sampling should be done as planned. Patients should be instructed to record the time of study drug administration and the dose actually taken in the patient diary. Following the primary database lock, patients will not be required to complete the patient diary.

5.1.1. Investigational Product

In this protocol, the investigational product is YH25448.

5.1.2. Non-investigational Product

In this protocol, the non-investigational product is none.

5.1.3. Identification

The Sponsor will supply YH25448 as tablets for oral dosing. Additional information about the investigational product may be found in the Investigators' Brochure.

Table 6. Investigational Products Description

Code	Dosage form and strength	Manufacturer
YH25448	*10, 20, 40, 80 mg tablet*	Yuhan Corporation

5.1.4. Packaging and Labeling

YH25448 tablets will be packed in aluminum bags or Alu-Alu PTP. Packed aluminium bags or Alu-Alu PTP of YH25448 will be dispensed at each dispensing visit depending on the dose. The packaging includes aluminium bags or Alu-Alu PTP, zipper bags or carton, and a label. The labels of Investigational Products will be in the local language and comply with the legal requirements of each country. The label will include the following information: the Name of the Sponsor, Study Code, For Clinical trial use only and /or any other market specific requirements.

All investigational products should be kept in a secure place under appropriate storage conditions. The investigational product label on the pack specifies the appropriate storage.

5.1.5. Handling and Dispensing

It is the responsibility of the investigator to ensure that investigational product is only dispensed to study patients. The investigational product must be stored in a secure area and dispensed only from official study centers by authorized personnel in accordance with local regulations.

The investigator should ensure that the investigational product is stored in accordance with the environmental conditions (temperature, light etc.) recommended by the Sponsor. The sealed packages of YH25448 in the form of tablet should be stored at room temperature.

Investigators and site staff are reminded to check temperatures and ensure that thermometers are working correctly, as required for proper storage of investigational products. Any temperature excursions should be reported to immediately.

If concerns regarding the quality or appearance of the investigational product arise, do not use it and contact the Sponsor immediately.

The investigator or designee must maintain an accurate record of the shipment and dispensing of study drug per local institutional guidelines. The study drugs are for investigational use only and are to be used only within the context of this study. Drug accountability will be noted by

the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study drug and packaging on a regular basis, at the next visit of study drug dispense and at the end of the study or at the time of study drug discontinuation.

5.2. Method of Assigning Patients to a Treatment

The treatment assignment will be controlled centrally.

5.3. Safety Review Committee

After each dose level during the dose escalation phase of the study, the SRC will evaluate the available safety, tolerability and PK of YH25448 to decide the next dose. The SRC may be convened in case of necessity to review the data and discuss each following mentioned in Section 5.3 to decide on the topic after the completion of the dose escalation phase.

The SRC will consist of:

- Sponsor Study Physician, who will chair the committee, or delegate
- Principal Investigator or delegate from each investigational site who participates in each cohort

In addition, other physicians from the following may be invited:

- Medical Monitor or delegate

Study PK Scientist, Study Statistician may also be invited as appropriate. Further internal or external experts may be consulted by the SRC as necessary. The SRC Charter for this study will define the exact membership and who should be present for decisions to be made.

Once there are at least 3 evaluable patients for dose escalation phase at a dose level the SRC will review and assess all available safety data from the cohort together with available PK data to make a decision on the dose for the next cohort of patients. Any dose interruptions and reductions will be taken into account. It is planned to conduct the SRC meeting regularly, but the frequency may be adjusted according to patient enrollment rate, emerging data, etc.

The decision may be to:

- Proceed with dose escalation refer to Section 4.1.2.
- Expand the cohort to a maximum of 6 evaluable patients (except at MTD or an effective dose as agreed by SRC if additional patients are recruited,)
- De-escalate the dose either to a previous lower dose level or to a lower intermediary dose level

- Stop the dose escalation phase of the study
  - Initiate dose expansion phase and dose extension phase
  - Evaluate alternative dosing frequencies/intermittent dose schedules
  - Add additional patients at MTD
  - Evaluate the benefit and risk by reviewing safety at the expansion phase and dose extension phase

When there are other patients that are ongoing at the time of this review, the SRC may decide to defer their decision until these further patients become evaluable.

Any patient started on treatment in error, as he/she failed to comply with all of the selection criteria but meets the criteria of an evaluable patient, will be reviewed on a case by case basis by the SRC to determine if the patients data should be included or excluded in the decision for dose escalation.

The decisions and decision-making of the SRC on the next dose level will be documented and provided to the investigators prior to dosing any new patients.

5.4. Dose Modification

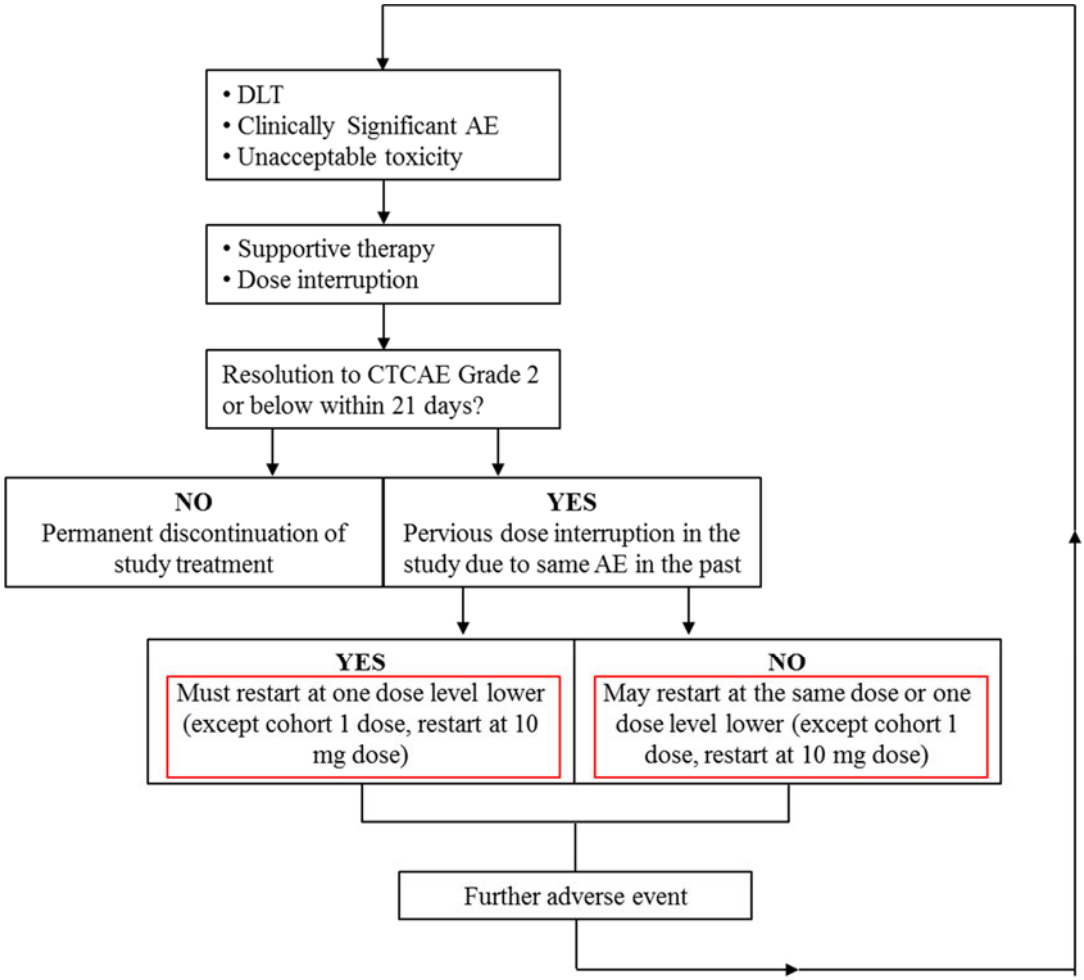
5.4.1. Toxicity management and dose modifications to YH25448

If a patient experiences a CTCAE grade 3 and/or unacceptable toxicity including a DLT not attributable to the disease or disease-related processes under investigation, dosing will be interrupted and supportive therapy administered as required in accordance with local practice/guidelines. Patients with QTc prolongation fulfilling the DLT criteria (i.e. confirmed QTc prolongation to >500 msec absolute or a > 60 msec increase from baseline) should have study treatment interrupted and regular ECGs performed until resolution to baseline. If the QTc prolongation toxicity does not resolve to ≤ grade 1 within 21 days the patient will be permanently withdrawn from study treatment.

5.4.1.1. Escalation and Expansion patients

If any other toxicity resolves or reverts to ≤ CTCAE grade 2 within 21 days of onset and the patient is showing clinical benefit, treatment with YH25448 may be restarted at the same dose or one dose level lower which has been declared safe and tolerable by the SRC. Dose modification will follow the rules below described in Figure 2 and may be agreed between the investigator and Sponsor Study Physician as needed.

Figure 2. Dose modifications for toxicity of YH25448



If any other toxicity does not resolve to ≤ CTCAE grade 2 after 21 days, then the patient should be withdrawn from the study and observed until resolution of the toxicity.

On resolution of toxicity within 21 days:

- If a further episode of the same AE subsequently requires dose interruption, YH25448 must restart at one dose level lower which has been declared safe and tolerable, in case of Cohort 1, restart may be at 10 mg on resolution /improvement of the AE at the discretion of the Investigator.

- If a different AE subsequently requires dose interruption, YH25448 may restart at the same or one dose level lower which has been declared safe and tolerable, in case of Cohort 1, restart may be at 10 mg on improvement of the AE at the discretion of the Investigator.

For particular cases which don't follow the dose modification rules as defined in Figure 2, an agreement should be reached with the Sponsor Study Physician.

5.4.1.2. Extension patients

If any other toxicity resolves or reverts to dose modification rules as defined, treatment with YH25448 may be restarted at the same dose or a lower dose following discussion and agreement with the Sponsor Study Physician or delegated study physician as needed. There will be no individual modifications to dosing schedule in response to toxicity, only potential dose reduction or dose interruption.

If the toxicity does not resolve to ≤CTCAE grade 2 after 21 days, then the patient should be withdrawn from the study and observed until resolution of the toxicity.

On resolution of toxicity within 21 days:

- If an AE subsequently requires dose interruption, YH25448 may restart at the same dose or the reduced dose, on resolution/improvement of the AE at the discretion of the Investigator

5.4.1.3. Patients Outside Korea

5.4.1.3.1. YH25448 dose reduction levels in response to toxicity

- Subjects who start YH25448 at a dose of 240 mg (Level 1), may be dose reduced one dose level to 160 mg (Level -1) in response to study drug toxicity.

- Subjects who start YH25448 at a dose of 320 mg (Level 2), may be dose reduced one dose level to 240 mg (Level 1) or two dose levels to 160 mg (Level -1) in response to study drug toxicity.

- All doses are given on a once daily schedule

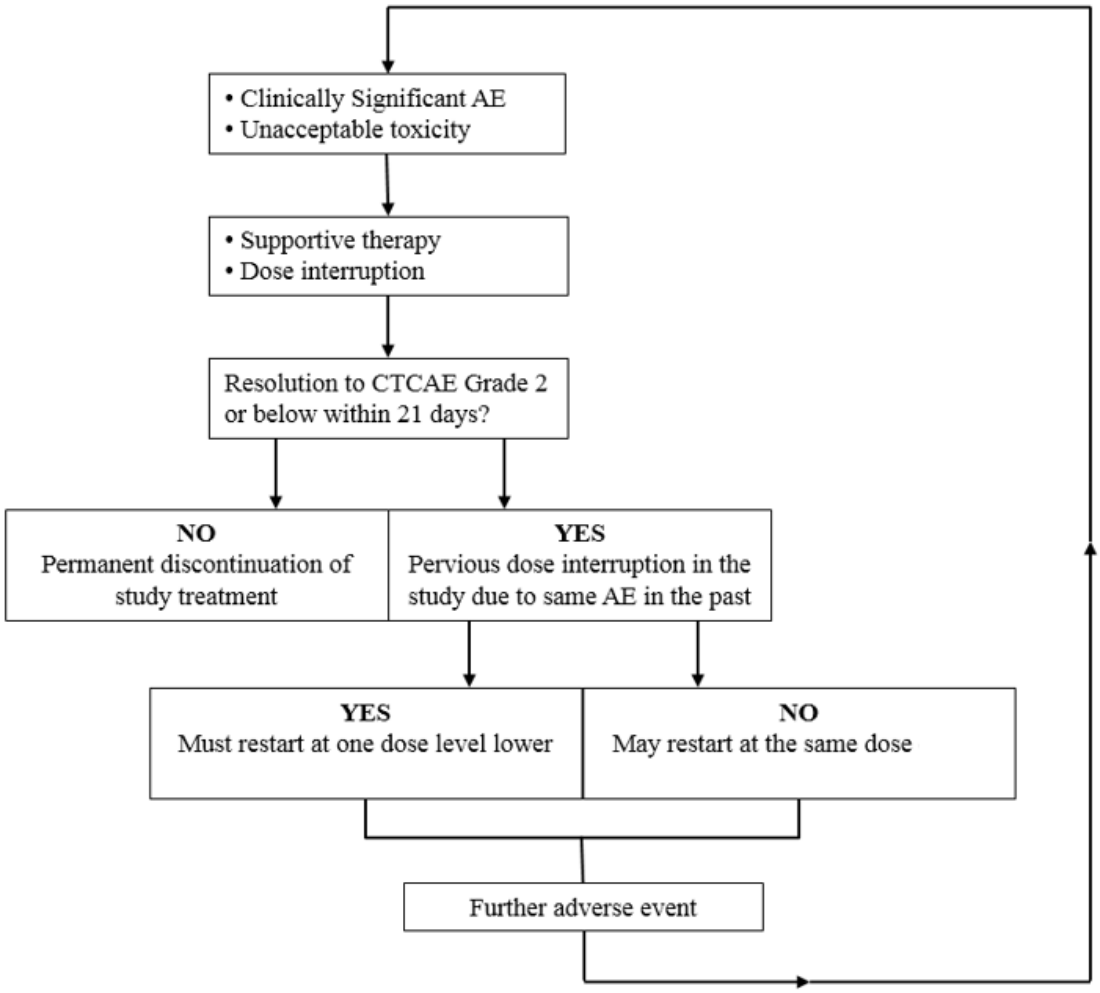
5.4.1.3.2. YH25448 dose modification guidelines for toxicities

If a patient experiences a CTCAE version 4.03 Grade 3 toxicity while receiving YH25448, or other unacceptable toxicity, dosing with YH25448 will be interrupted and supportive therapy administered as required in accordance with local practice/guidelines. If the toxicity resolves or reverts to ≤CTCAE Grade 2 within 21 days of onset and the patient is showing clinical benefit, treatment with YH25448 may be restarted at the same dose level. Dose modification will follow the rules below described in Figure 3 and may be agreed between the investigator and medical monitor as needed.

Figure 3. Dose modifications for toxicity of YH25448 in Part D

If a patient restarts YH25448 upon resolution of toxicity within 21 days:

- If a further episode of the same AE subsequently requires dose interruption, YH25448 must be restarted at one dose level lower. In this case, if the patient is already at Dose Level -1 then the study drug must be permanently discontinued.



- If a different AE subsequently requires dose interruption, YH25448 may be restarted at the same or lower dose.

Patients with QTc prolongation fulfilling DLT criteria (ie, confirmed QTc prolongation to >500 msec absolute or a >60 msec increase from baseline) should have the study treatment interrupted and regular ECGs performed until resolution to baseline. If the QTc prolongation toxicity does not resolve to ≤ Grade 1 within 21 days the patient will be permanently withdrawn from study treatment.

5.4.1.4. All Patients

Guidelines for management of EGFR inhibitor-induced corneal ulceration, interstitial lung disease, cardiac dysfunction, rash-related toxicities and diarrhea are provided below in Sections 5.4.1.4.1, 5.4.1.4.2, 5.4.1.4.3, 5.4.1.4.4, and 5.4.1.4.5, respectively.

5.4.1.4.1. Guidelines for the management of YH25448 induced corneal ulceration

Patients experiencing corneal ulceration or Interstitial Lung Disease (ILD) will not be permitted to restart study treatment.

Ophthalmic assessment, including slit lamp examination, fundoscopic examination, eye examination and other tests by investigator's judgement will be performed at screening and should be repeated if a patient experiences any visual symptoms (including blurring of vision), with additional tests if clinically indicated. Depending on the severity of visual symptoms, investigator should observe 5.4.1 for dose interruptions and reductions.

5.4.1.4.2. Guidelines for the management of YH25448 induced interstitial lung disease

Patients with a past medical history of interstitial lung disease, drug-induced interstitial lung disease, radiation pneumonitis which required steroid treatment, or any evidence of clinically active interstitial lung disease will be excluded from participation in this study. Patients with any grade of interstitial lung disease (ILD) will stop YH25448 and be treated as medically indicated. If new or worsening pulmonary symptoms (e.g., dyspnoea) or radiological abnormality suggestive of interstitial lung disease is observed, an interruption in study treatment dosing is recommended, and the Sponsor study team should be informed. Investigator will perform a full diagnostic workup (including high-resolution computed tomography (HRCT), blood and sputum culture, haematological parameters, bronchoscopy with biopsy as needed) to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of interstitial lung disease should be considered and study treatment permanently discontinued. In the absence of a diagnosis of interstitial lung disease study treatment may be restarted following consultation with the Sponsor Study Physician.

5.4.1.4.3. Guidelines for the management of YH25448 induced cardiac dysfunction

Patients with confirmed symptomatic cardiac dysfunction (Grade ≥ 3 left ventricular systolic dysfunction as defined by CTCAE) will be discontinued from study treatment. Asymptomatic declines in LVEF or elevated TnI will be handled with the process described in detail in appendix B. If the LVEF is reported as a range, the average should be taken. If an investigator is concerned that an adverse event may be related to cardiac dysfunction, an additional LVEF measurement may be performed. Until the primary database lock, LVEF will be monitored at screening, every 12 weeks , and TnI will be monitored at screening, every visit and as clinically indicated.

SRC will review all potential cases of left ventricular systolic dysfunction (See appendix B of this Clinical Study Protocol).

5.4.1.4.4. Guidelines for the prevention, monitoring, and management of YH25448 induced rash-related adverse events

Prophylactic treatment

Starting at the initiation of study drug dosing and continuing during dosing subjects are to be instructed to:

- use a thick, alcohol-free emollient cream (eg, glycerin and cetomacrogol cream) to prevent dry skin and pruritis
- avoid immersion in hot water / detergent / solvents
- avoid exposure to sunlight.
- use broad-spectrum sunscreen (containing titanium dioxide or zinc oxide) with a skin protection factor (SPF) ≥15 if sunlight exposure cannot be avoided

Reactive management

The following interventions and the stepwise algorithm shown in Table 7 are to be used for EGFR inhibitor-induced rash

  - Topical corticosteroids (eg, hydrocortisone 2.5% cream)
  - Topical antibiotic (eg. clindamycin 1% gel)
  - Topical corticosteroids and systemic antibiotics (minocycline 100 mg bid or first generation cephalosporine (avoid CYP3A4 inhibitors)).
  - For pruritic lesions, the use of cool compresses and oral antihistamine agents may be helpful.
  - For fissuring, the use of Monsel's solution (ferric subsulfate solution), silver nitrate, or zinc oxide cream is advised.
  - For desquamation, thick emollients and mild soap are recommended.
  - For paronychia, antiseptic soaks and local potent corticosteroids in addition to oral antibiotics are recommended and, if no improvement is seen, a dermatology or surgery consultation is recommended.

- For infected lesions, bacterial and fungal culturing followed by the appropriate culture-driven systemic or topical antibiotics is indicated.

- Consult with a dermatologist if the rash is severe, atypical in appearance, or distribution, or does not improve within 2 weeks of treatment.

Table 7. Stepwise Algorithm for Management of Rash

Step	Rash grading[c]	Management of Rash	YH25448 Dose Adjustment[a,b,]
1	1	Initiate prophylactic regimen if not already started and add reactive therapies as above. Reassess after 2 weeks; if rash worsens or does not improve, proceed to Step 2	Continue current dose. Reassess after 2 weeks; if rash does not improve, proceed to Step 2
2	2	Initiate prophylactic regimen if not already started, including topical corticosteroids and systemic antibiotics as above.[d] Reassess after 2 weeks; if rash does not improve, proceed to Step 3	Consider reducing dose by one dose level Reassess after 2 weeks; if rash does not improve, proceed to Step 3
3	3 or intolerable Grade 2	Initiate prophylactic regimen if not already started, moderate strength topical corticosteroids and systemic antibiotics as above plus prednisone (0.5 mg/kg) for 7 days. Consider low doses of isotretinoin (20-30 mg/day). Consider obtaining dermatology consultation and manage rash per dermatologist's recommendation.	Temporarily interrupt treatment until rash improves ≤ Grade 2 or resolves, then follow steps outlined for the appropriate grading. Reassess after 2 weeks; if rash worsens or does not improve, permanently discontinue treatment.

[a] If drug must be withheld due to toxicity for 2 consecutive doses, then study drug cannot be restarted without prior permission from the Sponsor medical monitor.
[b] Resolution defined as: ≤Grade 1 non-hematologic toxicity or back to baseline
[c] Grading per NCI CTCAE (Version 4.03)
ADL: Active Daily Life

5.4.1.4.5. Guidelines for the monitoring, and management of YH25448 induced diarrhea

- If patients experience diarrhea, they should be encouraged to drink 8 to 10 large glasses of clear liquids per day while on study in order to maintain adequate hydration. Maintenance of electrolyte balance using electrolyte containing drinks, broth, and clear juices should be considered.

  If an infectious cause of the diarrhea is suspected, perform stool testing and administer antibiotic therapy (avoid CYP3A4 inhibitors) as appropriate.

- General dietary measures to limit impact of diarrhea include:
  - Stop all lactose-containing products in patients with evidence of lactose intolerance
  - Eat frequent small meals if experiencing increased frequency of stools
  - Consider low-fat regimen enriched with bananas, rice, applesauce, and toast

- CTCAE version 4.03 Grade 1: Loperamide (4 mg at first onset, then 2 mg every 2-4 hours until symptom free for 12 hours). Fluid intake of at least 2 L as described above. ***Study treatment*:** should be continued at the same dose.

- CTCAE version 4.03 Grade 2: Loperamide (4 mg at first onset, then 2 mg every 2-4 hours until symptom free for 12 hours), or consider diphenoxylate and atropine formulations (e.g., Lomotil®). Fluid intake of at least 2 L as described above. Monitor patient closely and consider intravenous hydration. ***Study treatment*:** If not improved to Grade ≤1 within 24 hours despite use of loperamide, hold treatment until Grade ≤1. If diarrhea of Grade >1 recurs after initial improvement, consider reduction by one dose level

- CTCAE version 4.03 Grade 3: Oral therapy with diphenoxylate and atropine formulations (eg, Lomotil®), or tincture of opium. Fluid intake of at least 2 L should be maintained as described above, intravenously if necessary. Consider use of octreotide (Sandostatin®) 100-150 microgram (μg) subcutaneously twice daily with escalation to 500 μg three times daily. Consider hospitalization if does not improve to Grade ≤2 within 24 hours, or in presence of fever, abdominal pain, etc. ***Study Treatment:*** Hold therapy. Upon resolution to Grade ≤1, resume therapy with consideration of reduction by one dose level.

- CTCAE version 4.03 Grade 4: Maximal inpatient fluid and nutritional support, antibiotics as indicated in judgment of investigator for fever, leucocytosis, marked dehydration, etc. ***Study Treatment***: Hold until Grade ≤1. Mandatory dose reduction by one dose level.

5.4.2. Assessment timings if dosing is interrupted

All other assessments, including laboratory safety assessments, vital signs and RECIST 1.1 should continue to be performed as per study plan, relative to the baseline assessments.

5.5. Treatment compliance and accountability

The investigational product should only be used as directed in this protocol. Details of treatment with investigational product for each patient will be recorded in the Case Record Form.

Patients should return all unused medication and empty containers to the investigator.

The study personnel at the investigational site will account for all drugs dispensed and for appropriate return. The certificates of delivery and return should be signed.

Patients will be asked to record study drug dosing information including date and time of each medication intake in a patient diary provided by the Sponsor until the primary data base lock. Patients will bring the diaries, and all unused study drug and empty containers, to each study visit. Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the patient diary. Investigator must report as protocol

deviation if the subject of the study misses to take YH25448 4 days or more during one cycle, which is 21 days. This information regarding the study drug administration including all dosages prescribed and dispensed to the patient and all dose changes during the study must be captured in the source document and recorded on the Dosage Administration Record of eCRF at each visit until the primary database lock.

6. STUDY ASSESSMENTS AND PROCEDURES

6.1. Study Plan for Flow Chart/Time and Events Schedule

Assessments that are not mandatory for all patients are bracketed i.e. (X) in the Study Plan. The schedule of assessments may change in response to emerging data, updated assessment tables will be provided outside of the protocol.

Table 8. Part A: Dose Escalation Phase

Activities	Screening	Single Dose/Cycle0 (7±2 day Cycle)			Multiple Dose/Cycle1 (21 day Cycle)[1]			Cycle 2	Cycle onwards[2]	Unscheduled Visit[4]	After the primary DBL[24]	Discontinuation[5]	28 day follow-up[3]
Visit	1	2	3	4	5	6	7	8	9 onwards		Every 4 cycles		
Day	-28 to -1	D1	D2	D3	D1	D8	D15	D1	D1		D1		
Study Visit Window (Days)	N/A	0	0	0	0	±1	±3	0	±7	N/A	±14	+7	+7
Eligibility Assessments													
Informed consent[6]	X												
Demographics & baseline characteristics	X												
Medical / surgical history	X												
Inclusion / exclusion criteria	X												
T790M mutation status tumor sample[7] (mandatory)	X												
Physical Examination	X	X		X	X	X	X	X	X	X	(X)	X	X
ECOG	X	X			X			X	X	(X)	(X)	X	

Activities	Screening	Single Dose/Cycle0 (7±2 day Cycle)			Multiple Dose/Cycle1 (21 day Cycle)[1]			Cycle 2	Cycle onwards[2]	Unscheduled Visit[4]	After the primary DBL[24]	Discontinuation[5]	28 day follow-up[3]
Visit	1	2	3	4	5	6	7	8	9 onwards		Every 4 cycles		
Day	-28 to -1	D1	D2	D3	D1	D8	D15	D1	D1		D1		
Study Visit Window (Days)	N/A	0	0	0	0	±1	±3	0	±7	N/A	±14	+7	+7
Vital signs[8]	X	X	X	X	X	X	X	X	X	(X)	(X)	X	X
Height[9]	X												
Weight	X	X			X			X	X			X	
12-lead ECG[10]	X	X	X	X	X	X	X	X	X	(X)	(X)	X	
Echocardiography (or MUGA)[11]	X				12 weekly relative to first dose of multiple dosing					(X)	(X)	X	
Ophthalmologic assessment	X												
Hepatitis and HIV Screen	X												
Laboratory Test;[12]													
Clinical chemistry	X	X		X	X		X	X	X	(X)	(X)	X	
Hematology	X	X		X	X		X	X	X	(X)	(X)	X	
Urinalysis	X	X		X	X		X	X	X	(X)	(X)	X	
Pregnancy test[13] (female of child-bearing potential only)	X											X	
PK blood samples[14]		X	X	X	X	X	X	X					
Tumor assessment[15]													

Activities	Screening	Single Dose/Cycle0 (7±2 day Cycle)			Multiple Dose/Cycle1 (21 day Cycle)[1]			Cycle 2	Cycle onwards[2]	Unscheduled Visit[4]	After the primary DBL[24]	Discontinuation[5]	28 day follow-up[3]
Visit	1	2	3	4	5	6	7	8	9 onwards		Every 4 cycles		
Day	-28 to -1	D1	D2	D3	D1	D8	D15	D1	D1		D1		
Study Visit Window (Days)	N/A	0	0	0	0	±1	±3	0	±7	N/A	±14	+7	+7
RECIST 1.1 assessments	X							Every 2 cycles (relative to first dose of multiple dosing until progression)/ After 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.					
Blood sample													
Blood sample for cfDNA[17]	X[18]	X						Every 2 cycles (relative to first dose of multiple dosing until progression[19]					
Questionnaire[16]													
QLQ C-30	X				X			Every 2 cycles (relative to first dose of multiple dosing until progression)					
QLQ LC13	X				X			Every 2 cycles (relative to first dose of multiple dosing until progression)					
Others sampling procedures (optional))													
Genetic consent	(X)												
Tumor biopsy	(X)					(X)						(X)	
Genetic and biomarker blood sample	(X)												
CSF								(X) (once only)					
Drug supply and dosing													

Activities	Screening	Single Dose/Cycle0 (7±2 day Cycle)			Multiple Dose/Cycle1 (21 day Cycle)[1]			Cycle 2	Cycle onwards[2]	Unscheduled Visit[4]	After the primary DBL[24]	Discontinuation[5]	28 day follow-up[3]
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9 onwards**		**Every 4 cycles**		
Day	**-28 to -1**	**D1**	**D2**	**D3**	**D1**	**D8**	**D15**	**D1**	**D1**		**D1**		
Study Visit Window (Days)	**N/A**	**0**	**0**	**0**	**0**	**±1**	**±3**	**0**	**±7**	**N/A**	**±14**	**+7**	**+7**
Dispense study medication and subject diary					X			X	X		X (Dispense study medication only)		
Dose with YH25448[20]		X						Once daily oral administration					
Safety assessment													
Adverse Events[22]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X[25]	X	X

Table 9. Part B: Dose Expansion Phase

Activities	Screening	Multiple Dose/Cycle1 (21 day Cycle)[1]			Cycle 2 onwards[2]	Unscheduled Visit[4]	After the primary DBL[24]	Discontinuation[5]	28 day follow-up[3]	Follow up visit[23]
Visit	1	2	3	4	5 onwards		Every 4 cycles			
Day	-28 to -1	D1	D8	D15	D1		D1			
Study Visit Window (Days)	0	0	±3	±3	0 (Cycle 2) ±7 (After Cycle 3)	N/A	±14	+7	+7	±7
Eligibility Assessment										
Informed consent[6]	X									
Demographics & baseline characteristics	X									
Medical / surgical history	X									
Inclusion / exclusion criteria	X									
T790M mutation status tumor sample (mandatory)[7]	X									
Physical Examination	X	X	X	X	X	(X)	(X)	X	X	
ECOG	X	X			X		(X)	X		
Vital Signs[8]	X	X	X	X	X	(X)	(X)	X	X	
Height[9]	X									
Weight	X	X			X	(X)		X		

Activities	Screening	Multiple Dose/Cycle1 (21 day Cycle)[1]			Cycle 2 onwards[2]	Unscheduled Visit[4]	After the primary DBL[24]	Discontinuation[5]	28 day follow-up[3]	Follow up visit[23]
Visit	1	2	3	4	5 onwards		Every 4 cycles			
Day	-28 to -1	D1	D8	D15	D1		D1			
Study Visit Window (Days)	0	0	±3	±3	0 (Cycle 2) ±7 (After Cycle 3)	N/A	±14	+7	+7	±7
12-lead ECG[10]	X	X	X	X	X	(X)	(X)	X		
Echocardiography/ MUGA[11]	X	12 weekly relative to first dose				(X)	(X)	X		
Ophthalmologic assessment	X									
Hepatitis and HIV Screen	X									
Laboratory Test[12]										
Clinical chemistry	X	X		X	X	(X)	(X)	X		
Hematology	X	X		X	X	(X)	(X)	X		
Urinalysis	X	X		X	X	(X)	(X)	X		
Pregnancy test (female of child-bearing potential only)[13]	X							X		
PK blood samples		X	X	X	X (D1~D2 Cycle 2 only)					
Tumor assessment[15]										
RECIST 1.1 assessments	X				Every 2 cycles (relative to first dose of multiple dosing until progression) / After the					

Activities	Screening	Multiple Dose/Cycle1 (21 day Cycle)[1]			Cycle 2 onwards[2]	Unscheduled Visit[4]	After the primary DBL[24]	Discontinuation[5]	28 day follow-up[3]	Follow up visit[23]
Visit	1	2	3	4	5 onwards		Every 4 cycles			
Day	-28 to -1	D1	D8	D15	D1		D1			
Study Visit Window (Days)	0	0	±3	±3	0 (Cycle 2) ±7 (After Cycle 3)	N/A	±14	+7	+7	±7
	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.									
Blood sample										
Blood sample for cfDNA[17]	X[18]	X			Every 2 cycles at RECIST visit[19]					
Questionnaire[16]										
QLQ C-30	X	X			Every 2 cycles (relative to first dose of multiple dosing until progression)					
QLQ LC13	X	X			Every 2 cycles (relative to first dose of multiple dosing until progression)					
QLQ BN-20 (only BrM patients)	X	X			Every 2 cycles (relative to first dose of multiple dosing until progression)					
Others sampling procedures (optional))										
Genetic consent	(X)									
Tumor biopsy	(X)			(X)				(X)		
Genetic and biomarker	(X)									

Activities	Screening	Multiple Dose/Cycle1 (21 day Cycle)[1]			Cycle 2 onwards[2]	Unscheduled Visit[4]	After the primary DBL[24]	Discontinuation[5]	28 day follow-up[3]	Follow up visit[23]
Visit	**1**	**2**	**3**	**4**	**5 onwards**		**Every 4 cycles**			
Day	**-28 to -1**	**D1**	**D8**	**D15**	**D1**		**D1**			
Study Visit Window (Days)	**0**	**0**	**±3**	**±3**	**0 (Cycle 2) ±7 (After Cycle 3)**	**N/A**	**±14**	**+7**	**+7**	**±7**
blood sample										
CSF					(X) (once only)					
Drug supply and dosing										
Dispense study medication and subject diary		X			X		X (Dispense study medication only)			
Dose with YH25448[20]		Once daily oral administration								
Anti-cancer therapy survey										X
Safety assessment										
Adverse Events[22]	X	X	X	X	X	X	X	X	X	
Concomitant Medication	X	X	X	X	X	X	X[25]	X	X	

Table 10. Part C: Dose Extension Phase

Activities	Screening	Multiple Dose/Cycle1 (21 day Cycle)[1]			Cycle 2	Cycle3 onwards[2]	Unscheduled Visit[4]	After the primary DBL[24]	Discontinuation[5]	28 day follow-up[3]	Follow up visit[23]	Post Progression survival FU[21]
Visit	1	2	3	4	5	After 6		Every 4 cycles				Every 12 weeks
Day	-28 to -1	D1	D8	D15	D1	D1		D1				Telephone
Study Visit Window (Days)	0	0	±3	+7	±7	±7	N/A	±14	+7	+7	±7	±7
Eligibility Assessment												
Informed consent[6]	X											
Demographics & baseline characteristics	X											
Medical / surgical history	X											
Inclusion / exclusion criteria	X											
EGFR Mutation test (In case of 1st line therapy cohort)	X											
T790M mutation status tumor sample (mandatory)[7]	X											
Physical Examination	X	X	X	X	X	X	(X)	(X)	X	X		
ECOG	X	X			X	X	(X)	(X)	X			

Activities	Screening	Multiple Dose/Cycle1 (21 day Cycle)[1]			Cycle 2	Cycle3 onwards[2]	Unscheduled Visit[4]	After the primary DBL[24]	Discontinuation[5]	28 day follow-up[3]	Follow up visit[23]	Post Progression survival FU[21]
Visit	**1**	**2**	**3**	**4**	**5**	**After 6**		**Every 4 cycles**				**Every 12 weeks**
Day	**-28 to -1**	**D1**	**D8**	**D15**	**D1**	**D1**		**D1**				**Telephone**
Study Visit Window (Days)	**0**	**0**	**±3**	**+7**	**±7**	**±7**	**N/A**	**±14**	**+7**	**+7**	**±7**	**±7**
Vital Signs[8]	X	X	X	X	X	X	(X)	(X)	X	X		
Height[9]	X											
Weight	X	X			X	X	(X)		X			
12-lead ECG[10]	X	X	X	X	X	X	(X)	(X)	X			
Echocardiography/ MUGA[11]	X	12 weekly relative to first dose						(X)	X			
Ophthalmologic assessment	X											
Hepatitis and HIV Screen	X											
Laboratory Test[12]												
Clinical chemistry	X	X		X	X	X	(X)	(X)	X			
Hematology	X	X		X	X	X	(X)	(X)	X			
Urinalysis	X	X		X	X	X	(X)	(X)	X			
Pregnancy test (female of child-bearing potential only)[13]	X								X			

Activities	Screening	Multiple Dose/Cycle1 (21 day Cycle)[1]			Cycle 2	Cycle3 onwards[2]	Unscheduled Visit[4]	After the primary DBL[24]	Discontinuation[5]	28 day follow-up[3]	Follow up visit[23]	Post Progression survival FU[21]
Visit	**1**	**2**	**3**	**4**	**5**	**After 6**		**Every 4 cycles**				**Every 12 weeks**
Day	**-28 to -1**	**D1**	**D8**	**D15**	**D1**	**D1**		**D1**				**Telephone**
Study Visit Window (Days)	**0**	**0**	**±3**	**+7**	**±7**	**±7**	**N/A**	**±14**	**+7**	**+7**	**±7**	**±7**
PK blood samples		X	X	X								
Tumor assessment[15]												
RECIST 1.1 assessments	X	Every 2 cycles (relative to first dose of multiple dosing) until progression / 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.										
Blood Sample												
Blood sample for cfDNA[17]	X[18]	X	Every 2 cycles at RECIST visit[19]									
Survival and anti-cancer therapy survey[21]											X	X
Questionnaire[16]												
QLQ C-30	X	X	Every 2 cycles (relative to first dose of multiple dosing) until progression									
QLQ LC13	X	X	Every 2 cycles (relative to first dose of multiple dosing) until progression									
QLQ BN-20 (only BrM patients)	X	X	Every 2 cycles (relative to first dose of multiple dosing) until progression									
Others sampling procedures												

Activities	Screening	Multiple Dose/Cycle1 (21 day Cycle)[1]			Cycle 2	Cycle3 onwards[2]	Unscheduled Visit[4]	After the primary DBL[24]	Discontinuation[5]	28 day follow-up[3]	Follow up visit[23]	Post Progression survival FU[21]
Visit	**1**	**2**	**3**	**4**	**5**	**After 6**		**Every 4 cycles**				**Every 12 weeks**
Day	**-28 to -1**	**D1**	**D8**	**D15**	**D1**	**D1**		**D1**				**Telephone**
Study Visit Window (Days)	**0**	**0**	**±3**	**+7**	**±7**	**±7**	**N/A**	**±14**	**+7**	**+7**	**±7**	**±7**
(optional)												
Genetic consent	(X)											
Tumor biopsy	(X)			(X)					(X)			
Genetic and biomarker blood sample	(X)											
CSF						(X) (once only)						
Drug supply and dosing												
Dispense study medication and subject diary		X			X	X		X (Dispense study medication only)				
Dose with YH25448[20]		Once daily oral administration										
Safety assessment												
Adverse Events[22]	X	X	X	X	X	X	X	X	X	X		
Concomitant Medication	X	X	X	X	X	X	X	X[25]	X	X		

CT: Computerized tomography, cfDNA: circulating free tumor DNA, ECG: Electrocardiogram, EORTC: European Organization for Research and Treatment of Cancer, MRI: Magnetic resonance imaging, MUGA: Multiple gated acquisition scan, PK: Pharmacokinetics, RECIST: Response Evaluation Criteria in Solid Tumors,

QLQ: Quality of Life Questionnaire.

1. A treatment cycle is defined as 21 days for the purposes of scheduling procedures and evaluations. There will be no scheduled break between cycles.
2. Study visits will occur on Day 1 of every cycle until Cycle 7 and every other cycle from Cycle 7 onwards for dose escalation and dose expansion. But study visits for dose extension will occur on Day 1 of every other cycle from Cycle 3 onwards (C1D1, C2D1, C3D1, C5D1, C7D1…).
3. 28-day Follow-up visit will be scheduled 28 days (+7 days) after discontinuation visit.
4. Unscheduled visits can be arranged if necessary. Study procedures will be at the discretion of the investigator.
5. All patients will attend a discontinuation visit within 7 days of permanent discontinuation of study drug, where all procedures for the discontinuation visit will be performed. The discontinuation visit should occur before the start of a new treatment and the reason should be documented on the eCRF. After the primary database lock, only clinically indicated tests by the investigator's judgement will be performed.
6. Signed informed consent must be obtained before the patient undergoes any study-specific procedures.
7. T790M mutation must be centrally confirmed within 28 days before starting administration of YH25448 and a tissue sample must be collected after the progression disease on the therapy recently (the patients with locally confirmed T790M mutation positive also can be enrolled for Part C 2nd line treatment cohort). During the screening, if there is a sample which is meet the conditions required above, an archived tissue sample is able to be used for T790M mutation confirmation (Only in part A, dose escalation phase, if an archive sample is collected after progression disease on authorized EGFR TKIs therapy regardless of the recent treatment, the sample is able to be used for T790M mutation confirmation.) The Screening period can be extended to 42 days, if required, for the T790M tumor mutation testing only. For the dose extension phase, collected tissue samples must be submitted for central confirmation prior to the start of YH25448.
8. Vital signs (heart rate, blood pressure and body temperature) will be performed at each scheduled visit as per section 6.2.3. These will be obtained after the patient has rested for 10 minutes. The date and time of the assessment should be recorded.
9. Height will be taken only at Screening.
10. 12-lead ECGs (in triplicate, approximately 2 minutes apart), with central reading by a cardiologist, will be performed as planned schedule in section 6.2.4. ECG for dose escalation phase will be performed at screening and on Day 1 Cycle 0: pre-dose, 1,2,4,6,8,10,12, 24 hrs(Day 2) and 48 hrs(Day3) post-dose. Day 1, 8 and 15 Cycle 1 for all phase: pre-dose. Day 1 Cycle 1 for dose expansion and extension phases: 2, 4 hrs post-dose. Day 1 Cycle 2 for dose escalation and expansion phases: pre-dose, 1, 2, 4, 6, 8, 10, 12 and 24(Day 2) post dose. On Day 1 of each subsequent visits: one assessment at any time during day and discontinuation visit. For ECGs recorded in parallel with blood sampling for PK analysis, the blood sample should be collected subsequently after the triplicate ECGs have been performed. From Cycle 3 to the primary database lock, an ECG will be performed on Day 1 of each scheduled visit cycle for safety monitoring but it will not be time-matched and can be performed regardless of dosing time.
11. LVEF will be assessed using an echocardiogram or MUGA at Screening and every 12±**1** weeks until the primary database lock visit. Additional assessment may be performed if clinically indicated. If the result of TnI is positive, it will be re-tested by central laboratory within 3 days before permanent discontinuation of study treatment. For any patient who has at least one echocardiogram or MUGA that is considered abnormal by local assessment, the Sponsor collects all echocardiograms or MUGAs (obtained at Screening and all subsequent assessments) for the purpose of a central read.
12. Clinical Laboratory tests are not required if acceptable Screening is performed within 7 days prior to administration of study drug, unless the patient's clinical condition has changed significantly. But if the results of lab.test within 7 days prior to administration of study drug is not available, clinical lab.test should be performed at baseline visit before IP intake. If needed, any clinical laboratory tests may be performed for safety evaluation of patients additionally.
13. At Screening and Discontinuation visit, all females of childbearing potential should complete a urine/serum pregnancy test per the practice of the center. Repeat as necessary during the treatment period if clinically indicated.

14. PK blood samples will be taken as per scheduled time on table 13 at section 6.3.1. Hospitalization for Day 1, 2, and 3 Cycle 0 and Day 1, 2 Cycle 2 is required for PK blood sampling. Patients will take the first dose at the center; if the patient vomits the dose it should not be replaced but the time of vomiting should be captured in source document. PK blood sampling should be done as planned.
15. The patient must have at least one lesion, has not been previously irradiated that can be accurately measured. Radiological and clinical tumor assessments will be performed at Screening, and every 2 cycles (± 7 days) until objective disease progression using the RECIST 1.1 or, for patient who stop taking the study drug without disease progression until disease progression or before subsequent anticancer therapy begins.

Baseline tumor assessment during screening must be performed within 28 days of the start of study drug. If there is only one measurable lesion and it should be chosen for biopsy, tumor assessment should be performed at least 14 days after the biopsy. If the local treatment was given for brain metastases, baseline brain CT/MRI must be taken after the treatment has been completed.

If there is no brain lesion before screening period, in Part A, brain CT/MRI can be performed at screening if suspected brain metastasis. In Part B and C, brain CT.MRI will be performed after confirmation of T790M + centrally (EGFR for 1st line treatment cohort only). Tumor assessment for the brain lesion will be performed every two cycles (± 7days), if the subject has the brain lesion at the baseline.

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. The independent central review will not be performed anymore.

16. EORTC QLQ-C30 and EORTC QLQ LC13, QLQ BN20 (BrM patients only) should be completed prior to any other visit-specific procedures.
17. Until the primary database lock, Blood samples for cfDNA analysis will be collected on the same day of scheduled and any unscheduled tumor assessment as possible.
18. To be taken during the screening period prior to the first drug administered.
19. Collect every 2 cycles (± 7 days) up to and including progression (corresponding with the RECIST 1.1 assessments and continuing after treatment discontinuation in absence of disease progression).
20. All screening procedures and laboratory results must be available and reviewed before the patient receives the first dose of study drug. YH25448 should be taken orally QD at approximately the similar time under fasting before meal, with a glass of water. The time of study drug administration for specific days should be recorded in the patient diary which is distributed with study drug excluding the C0D1 visit in part A.
21. All patients correspond to RP2D who are confirmed disease progression for selected extension dose cohorts of dose expansion phase and all dose extension phase will be followed for survival and any post-study anticancer treatment via at least a telephone contact every 6 weeks relative to progression until death or withdrawal of consent. After the primary database lock, the survival and any post-study anticancer treatment will be followed every 12 weeks.
22. Unless the patients withdraw consent, they must be followed for AEs from the date of informed consent until 28 days after the last dose of study treatment. In the event of serious or study drug-related toxicities, the patient will be followed until resolution or stabilization.
23. All patients who discontinue study drug without progression will continue to be followed any anti-cancer therapy and perform tumor assessment every 2 cycles (±7 days) until disease progression or before subsequent anticancer therapy begins. If patients continue to receive the study drug after intracranial lesion has shown clinical benefit regardless of progression for extracranial lesion, tumor assessment will be continued every 2 cycles until progression for intracranial lesion. 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.
24. After the primary database lock, only clinically indicated tests will be performed by the investigator's judgement. Only the minimum data (ie, whether performed, date, etc.) will be collected in the EDC.

25. After the primary database lock, only concomitant medications related to SAEs will be collected.

Table 11. Part D: Patients Outside Korea

Activities	Screening	Single Dose/Cycle 0 (7±2 day Cycle)			Multiple Dose/Cycle1 (21 day Cycle)[1]			Cycle 2 onwards [2]	Unscheduled Visit[4]	After the primary DBL	Discontinuation [5]	28 day follow -up[3]	Follow up visit[17]
Visit	1	2	3	4	5	6	7	8 onwards		Every 2 cycles			
Day	-28 to -1	D1	D 2	D 3	D 1	D 8	D1 5	D1		D1			
Study Visit Window (Days)	0	0	0	0	0	±3	±3	0 (Cycle 2) ±7 (Cycle 3 and onwards)	N/A	±7	+7	+7	±7
Eligibility Assessment													
Informed consent[6]	X												
Demographics & baseline characteristics	X												
Medical / surgical history	X												
Inclusion / exclusion criteria	X												
Physical Examination	X	X[18]			X	X	X	X[18]	(X)	X	X	X	
ECOG	X	X[18]			X			X[18]		X	X		
Vital Signs[7]	X	X[18]	X	X	X	X	X	X[18]	(X)	X	X	X	
Height[8]	X												

Activities	Screening	Single Dose/Cycle 0 (7±2 day Cycle)			Multiple Dose/Cycle1 (21 day Cycle)[1]			Cycle 2 onwards [2]	Unscheduled Visit[4]	After the primary DBL	Discontinuation [5]	28 day follow -up[3]	Follow up visit[17]
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8 onwards**		**Every 2 cycles**			
Day	**-28 to -1**	**D1**	**D 2**	**D 3**	**D 1**	**D 8**	**D1 5**	**D1**		**D1**			
Study Visit Window (Days)	**0**	**0**	**0**	**0**	**0**	**±3**	**±3**	**0 (Cycle 2) ±7 (Cycle 3 and onwards)**	**N/A**	**±7**	**+7**	**+7**	**±7**
Weight	X	X			X			X	(X)		X		
12-lead ECG[9] (See Table 12 below)	X	X			X			X	(X)	X	X		
Echocardiography/MUGA[10]	X				12±1 weekly relative to first dose				(X)		X		
Ophthalmologic assessment[11]	X												
Hepatitis and HIV Screen	X												
Laboratory Test[12]													
Clinical chemistry	X	X			X		X	X	(X)	X	X		
Hematology	X	X			X		X	X	(X)	X	X		
Urinalysis	X	X			X		X	X	(X)				
Pregnancy test (female of child-bearing potential only)[13]	X										X		
PK blood samples (See		X	X	X	X	X	X	X					

Activities	Screening	Single Dose/Cycle 0 (7±2 day Cycle)			Multiple Dose/Cycle1 (21 day Cycle)[1]			Cycle 2 onwards [2]	Unscheduled Visit[4]	After the primary DBL	Discontinuation [5]	28 day follow-up[3]	Follow up visit[17]
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8 onwards**		**Every 2 cycles**			
Day	**-28 to -1**	**D1**	**D 2**	**D 3**	**D 1**	**D 8**	**D1 5**	**D1**		**D1**			
Study Visit Window (Days)	**0**	**0**	**0**	**0**	**0**	**±3**	**±3**	**0 (Cycle 2) ±7 (Cycle 3 and onwards)**	**N/A**	**±7**	**+7**	**+7**	**±7**
Table 12 below)													
Pharmacogenetic blood sample (GSTM1)		X[19]											
Tumor assessment[14]													
CT/MRI RECIST 1.1 assessments	X							Every 2 cycles (relative to first dose of multiple dosing until progression) / 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.					
Drug supply and dosing													
Dispense study medication and subject diary					X			X		X (Dispense study medication only)			

Activities	Screening	Single Dose/Cycle 0 (7±2 day Cycle)			Multiple Dose/Cycle1 (21 day Cycle)[1]			Cycle 2 onwards [2]	Unscheduled Visit[4]	After the primary DBL	Discontinuation [5]	28 day follow -up[3]	Follow up visit[17]
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8 onwards**		**Every 2 cycles**			
Day	**-28 to -1**	**D1**	**D 2**	**D 3**	**D 1**	**D 8**	**D1 5**	**D1**		**D1**			
Study Visit Window (Days)	**0**	**0**	**0**	**0**	**0**	**±3**	**±3**	**0 (Cycle 2) ±7 (Cycle 3 and onwards)**	**N/A**	**±7**	**+7**	**+7**	**±7**
Dose with YH25448[15]		X						Once daily oral administration					
Survival and Anti-cancer therapy survey													X[20]
Safety assessment													
Adverse Events[16]	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medication	X	X	X	X	X	X	X	X	X	X[21]	X	X	

1. A treatment cycle is defined as 21 days for the purposes of scheduling procedures and evaluations. There will be no scheduled break between cycles.
2. Study visits will occur on Cycle 0 Days 1, 2, and 3 until a minimum of 6 Caucasian patients with evaluable PK have been enrolled, followed by study visits on Cycle 1 Days 1, 8, and 15, and followed by study visits on Cycle 2 Days 1 and 2 (see Table 11). Then study visits will occur on Day 1 of Cycle 3 and on Day 1 of every other cycle from Cycle 3 onwards (C3D1, C5D1, C7D1…).
3. 28-day Follow-up visit will be scheduled 28 days (+7 days) after discontinuation visit.
4. Unscheduled visits can be arranged if necessary. Study procedures will be at the discretion of the investigator.
5. All patients will attend a discontinuation visit within 7 days of permanent discontinuation of study drug, where all procedures for the discontinuation visit will be performed. The discontinuation visit should occur before the start of a new treatment and the reason should be documented on the eCRF.
6. Signed informed consent must be obtained before the patient undergoes any study-specific procedures.
7. Vital signs (heart rate, blood pressure and body temperature) will be performed at each scheduled visit as per Section 6.2.3. These will be obtained after the patient has rested for 10 minutes. The date and time of the assessment should be recorded.

8. Height will be taken only at Screening.
9. 12-lead ECGs (in triplicate, approximately 2 minutes apart), with central reading by a cardiologist, will be performed as planned schedule in Section 6.2.4 and Table 12. ECG for Part D will be performed at screening; pre-dose on Day 1 Cycle 0, Day 1 Cycle 1 and Day 1 Cycle 2; 2 hrs post-dose on Day 1 Cycle 0; 1, 2, 4 hrs post-dose on Day 1 Cycle 2; at any time during the day of Day 1 of Cycle 3 and of each subsequent visit onwards. For ECGs recorded in parallel with blood sampling for PK analysis, the blood sample should be collected subsequently after the triplicate ECGs have been performed. From Cycle 3 onward, an ECG will be performed on Day 1 of each scheduled visit cycle for safety monitoring but it will not be time-matched and can be performed regardless of dosing time. No central ECG reading will be required following the primary database lock.
10. LVEF will be assessed using an echocardiogram or MUGA at Screening and every 12**±1** weeks until the primary database lock visit. Additional assessment may be performed if clinically indicated. If TnI laboratory value exceeds the ULN, it will be re-tested by local laboratory within 3 days. If considered clinically significant, study treatment will be permanently discontinued after consultation with the Sponsor medical monitor. In Part D, central laboratory confirmation of TnI local laboratory value is not required. For any patient who has at least one echocardiogram or MUGA that is considered abnormal by local assessment, the Sponsor will collect all echocardiograms or MUGAs (obtained at Screening and all subsequent assessments) for the purpose of a central read. No ECHO/MUGA collection or central readings will be done following primary database lock.
11. Ophthalmologic assessment will be performed at Screening and should be repeated if a subject experiences any visual symptoms (including blurring of vision), with additional tests if clinically indicated.
12. Clinical Laboratory tests are not required if acceptable Screening is performed within 7 days prior to administration of study drug, unless the patient's clinical condition has changed significantly. But if the results of lab test within 7 days prior to administration of study drug is not available, clinical lab test should be performed at baseline visit before IP intake. If needed, any additional clinical laboratory tests may be performed for safety evaluation of patients.
13. At Screening and Discontinuation visit, all females of childbearing potential should complete a urine/serum pregnancy test per the practice of the center. Repeat as necessary during the treatment period if clinically indicated
14. Radiological and clinical tumor assessments will be performed at Screening, and every 2 cycles (± 7 days) until objective disease progression using the RECIST 1.1 or, for patient who stop taking the study drug without disease progression until disease progression or before subsequent anticancer therapy begins. Baseline tumor assessment during screening must be performed within 28 days of the start of study drug. If there is only one measurable lesion and it should be chosen for biopsy, tumor assessment should be performed at least 14 days after the biopsy. If local treatment was given for brain metastases, baseline brain MRI must be taken after the treatment has been completed. A brain MRI will be performed at screening and every two cycles (± 7 days), if the patient has a brain lesion at baseline. 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.
15. All screening procedures and laboratory results must be available and reviewed before the patient receives the first dose of study drug. YH25448 should be taken orally QD at approximately the similar time under fasting before meal, with a glass of water The time of study drug administration for specific days should be recorded in the patient diary which is distributed with study drug excluding the C0D1 visit in part D. No patient diaries are required following primary database lock.
16. Unless the patients withdraw consent, they must be followed for AEs from the date of informed consent until 28 days after the last dose of study treatment. In the event of serious or study drug-related toxicities, the patient will be followed until resolution or stabilization.
17. All patients who discontinue study drug without progression will continue to be followed any anti-cancer therapy and perform tumor assessment every 2 cycles (±7 days) until disease progression or before subsequent anticancer therapy begins. 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. Follow-up visits will be performed every 12 weeks

prior to Protocol Amendment 11. As of Protocol Amendment 11, follow-up visits will not be required for patients in Part D. Patients in Part D will not remain on study for radiological disease evaluations.

18. Physical examination, ECOG assessment and vital signs may be performed the day before a day during which a 10 h PK is planned.
19. Following informed consent, pharmacogenetic blood sample for assessment of genetic variants that encode drug-metabolizing enzyme GSTM1 may be collected at any time during the study although collection during screening is preferred. PK blood samples may also be utilized for this process. No GSTM1 samples will be collected after the primary database lock.
20. As of Protocol Amendment 11, follow-up visits will not be required for patients in Part D; overall survival and subsequent anticancer therapy data will not be collected.
21. After the primary database lock, only concomitant medications related to SAEs will be collected.

Table 12. Time and Events Schedule for Pharmacokinetic (PK), and ECG Assessments for Part D

Phase	Day	Time	Window	PK	ECG
Single Dose/Cycle 0	D1	Pre-dose	-15 min	X	X
		1 h	±10 min	X	
		2 h	±1 hours	X	X
		4 h	±1 hours	X	
		10 h	±1 hours	X	
	D2	24 h	±2 hours	X	
	D3	48 h	±2 hours	X	
Multiple Dose /Cycle 1	D1	Pre-dose	-15 min	X	X
	D8	Pre-dose	-15 min	X	
	D15	Pre-dose	-15 min	X	
Multiple Dose /Cycle 2	D1	Pre-dose	-15 min	X	X
		1 h	±10 min	X	X
		2 h	±1 hours	X	X
		4 h	±1 hours	X	X
		10 h	±1 hours	X	
	D2	Pre-dose (24 h)	-15 min	X	
Every other cycle from Cycle 3 onwards until the primary database lock	D1	Pre-dose	-15 min	X	X
Discontinuation					X

6.2. Safety Procedures

Prior to discharge from each in-patient and clinic visit, the Investigator or their deputy will be responsible for reviewing all available data including vital signs and ECG tracings.

For Parts A, B and C: After the primary database lock, only clinically indicated tests per investigator's judgement will be performed.

For Part D: After primary database lock, please refer to Schedule of Activities.

6.2.1. Enrollment and screening

At enrollment, each potential patient will provide informed consent prior to starting any study specific procedures (see appendix D of this Clinical Study Protocol for Ethics and Regulatory Requirements).

The Screening period can be extended to 42 days, if required, for the T790M tumor mutation testing only.

If a patient is a screen failure, but at some point in the future meets all of the eligibility criteria, the patient may be rescreened after a new informed consent has been obtained. Patients who are rescreened will be assigned a new screening number and will start a new screening phase. If the patient already have test result of T790M positive at previous screening, the collection of tumor tissue sample for T790M mutation is not required.

Recruitment into the study will be conducted in a controlled manner. If a patient withdraws from the study, then the enrolment code cannot be reused.

Demographic data and other characteristics will be recorded and will include date of birth or age, gender, race and/or ethnicity according to local regulations, smoking history.

A standard medical, medication and surgical history will be obtained with review of the selection criteria with the patient.

Each patient will undergo screening (see Study Plan Table 8, Table 9, Table 10 and Table 11) during the 28 days prior to admission to confirm eligibility (see Sections 4.2.1 and 4.2.2). Tumor assessments and other clinical data obtained as standard of care prior to consent may be used for the study provided the assessments fall within the protocol specified period prior to the first dose of study treatment.

6.2.2. Physical examination

A physical examination will be performed and include an assessment of the following: general appearance, skin, head and neck (including ears, eyes, nose and throat), respiratory, cardiovascular, abdomen, lymph nodes, thyroid, muscular-skeletal (including spine and extremities) and neurological systems (see Study Plan Table 8, Table 9, Table 10 and Table 11).

Performance status will be assessed at the visits as indicated in the Study Plan (see Table 8, Table 9, Table 10 and Table 11) according to ECOG criteria as follows:

0 Fully active, able to carry out all pre-disease activities without restrictions

1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light housework, office work

2 Ambulatory and capable of self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours

3 Capable of only limited self-care, confined to bed or chair more than 50% of waking Hours

4 Completely disabled, cannot carry on self-care, totally confined to bed or chair

5 Death

6.2.3. Vital signs

Blood pressure and pulse rate

Blood pressure and pulse rate will be measured after about 10 minutes rest. Assessments will be performed at the visits as shown in the Study Plan (See Table 8, Table 9, and Table 10).

For Part A, B, and C: Observation will be recorded at the following times:

- Screening
- First dosing day (Day 1 Cycle 0) for dose escalation phase: pre-dose, 1, 2, 4, 6, 8, 10, 12, 24 hours (Day 2) and 48 hours (Day 3) post-dose
- Day 1, Day 8 and Day 15, Cycle 1 (Multiple Dosing for all phases) : pre-dose
- First day of multiple dosing (Day 1, Cycle 1) for dose expansion and extension phases : 1, 2, 3 and 4 hours post-dose
- Day 1, Cycle 2 (Multiple dosing for dose escalation and expansion phases) : pre-dose, 1, 2, 4, 6, 8, 10, 12 and 24 hours (Day 2) post-dose
- On Day 1 of each subsequent scheduled cycle visit; one assessment at any time during day
- On occurrence of any cardiac AE
- Unscheduled Visit if needed
- Discontinuation visit

For Part D only: Observation will be recorded at the following times:

- Screening
- Pre-dose at each study treatment visit

- On occurrence of any cardiac AE
- Unscheduled Visit if needed
- Discontinuation visit
- 28 day follow-up visit

The timing and number of vital signs assessment may be altered depending on the emerging PK and safety profile.

A -2 h window at pre-dose (Day 1 in Cycle 0, Cycle 1 and Cycle 2) and a ±15 min window at 1-12 h; a ±1 h window at 24 h and 48 h; a -2 h window at pre-dose (Day 8 and Day 15 in Cycle 1). In Part D, the physical exam may be performed the day before a day during which a 10 h PK is planned.

Weight

Weight will be performed at screening and then at Day 1 of each subsequent scheduled cycles and at the discontinuation visit

Body temperature

Body temperature will be performed at screening and then at Day 1, Day 2 in Cycle 0, at Day 1, Day 8, Day 15 in Cycle 1, at Day 1 in Cycle 2 and at Day 1 of each subsequent scheduled cycles and at the discontinuation visit.

Height

Height will be assessed at screening only.

Any changes in vital signs should be recorded as an AE if applicable.

6.2.4. ECG

Resting 12-lead ECG

12-lead ECG will be performed at the visit indicated in the Study Plan for Parts A, B and C (see Table 8, Table 9 and Table 10).

- 12-lead ECGs will be recorded at the following times until the primary database lock: Screening
- First dosing day (Day 1 Cycle 0) for dose escalation phase: pre-dose, 1, 2, 4, 6, 8, 10, 12, 24 hours (Day 2) and 48 hours (Day 3) post-dose

- Day 1, Day 8 and Day 15, Cycle 1 (Multiple Dosing for all phases) : pre-dose
- First day of multiple dosing (Day 1 Cycle 1) for dose expansion and extension phases : 2 and 4 hours post-dose
- Day 1, Cycle 2 (Multiple dosing for dose escalation and expansion phases) : pre-dose, 1, 2, 4, 6, 8, 10, 12 and 24 hours (Day 2) post-dose
- On Day 1 of each subsequent scheduled cycle visit; one assessment at any time during day
- On occurrence of any cardiac AE
- Unscheduled Visit if needed
- Discontinuation visit

The timing and number of ECGs may be altered depending on the emerging PK and safety profile. For patients in Part D, see Table 12.

A -2 h window at pre-dose (Day 1 in Cycle 0, Cycle 1 and Cycle 2) and a ±15 min window at 1-12 h; a ±1 h window at 24 h; a -2 h window at pre-dose (Day 8 and Day 15 in Cycle 1).

12-lead ECGs will be obtained after the patient has been resting semi-supine for at least 10 minutes prior to times indicated. All ECGs should be recorded with the patient in the same physical position. For each time point three ECG recordings should be taken at about 2 minute intervals. A standardized ECG machine should be used and until the primary database lock. The patient should be examined using the same machine throughout the study if possible.

After paper ECGs have been recorded, the investigator or designated physician will review each ECG prior to discharge from the clinic and may refer to a local cardiologist if appropriate for immediate management of the patient. A paper copy and centrally confirmed results should be filed in the patient's medical records. If an abnormal ECG finding at screening or baseline is considered to be clinically significant by the investigator, it should be reported as a concurrent condition. For all ECGs details of rhythm, ECG intervals and an overall evaluation will be recorded.

All ECG data will also be collected digitally and will be transferred electronically for central analysis as described in the study specific ECG manual. Heart rate, PR, R-R, QRS and QT intervals will be determined and reviewed by an external cardiologist. (ECG result at screening should be read via paper ECG instead of central analysis.) After the primary database lock, the central analysis transmission procedure using the standard ECG machine will not be performed, but if necessary, it can be performed by site upon the investigator's judgement.

For Part D: After the primary database lock, a single ECG will be performed locally at each study visit.

6.2.5. Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, hematology and urinalysis will be taken at the visits as indicated in the Study Plan (see Table 8, Table 9, Table 10 and Table 11).

All the laboratory safety assessments will be conducted at local labs under fasted condition. Laboratory tests do not need to be repeated at baseline if the baseline visit is within 7 days of the screening sample.

Blood and urine samples for safety assessment will be collected at the following times:

- Screening
- First dosing day (Day 1 Cycle 0 for Parts A and D, Day 1 Cycle 1 for Parts B and C) : pre-dose (baseline)
- Day 3 Cycle 0 for Part A only : prior to discharge from hospital
- First day of multiple dosing, Day 1 Cycle 1 for Parts A and D : pre-dose
- Multiple dosing, Days 15 of Cycle 1 : pre-dose
- On Day 1 of each subsequent scheduled cycle visit : pre-dose
- Unscheduled Visit for some parameters if needed
- Discontinuation visit

The date of each collection will be recorded in the appropriate eCRF.

Following review of data from a group of patients the timing of blood samples may be adjusted for subsequent groups of patient. Additional sampling times may be added if indicated by the emerging PK and safety profile.

Laboratory values that meet the criteria for CTCAE Grade 3 or have changed significantly from baseline and are considered to be of clinical concern will be repeated/confirmed within 7 days and followed up as appropriate.

The following laboratory variables will be measured:

Clinical chemistry (Serum/Plasma)	Albumin ALT AST Alkaline phosphatase Total Bilirubin Calcium Total Creatinine Glucose HbA1C (screening and every 12 weeks) Magnesium Potassium Sodium Urea nitrogen Troponin I (screening and every visit)
Hematology(Blood)	Hemoglobin Leukocyte Hematocrit Red blood cell (RBC) count Absolute leukocyte differential count: Neutrophils Lymphocytes Monocytes Basophils Eosinophils Platelet count Reticulocytes
Urinalysis	Glucose Protein Blood (RBC and WBC)

HbA1C will be conducted at screening and every 12 weeks to first dose and discontinuation visit. And troponin I (TnI) will be conducted at screening and at the same visits at which blood laboratory tests are performed.

For Parts A, B and C: After the primary database lock, laboratory tests such as HbA1C, TnI, urinary tests, chemistry and hematology tests will be performed as clinically indicated per investigator discretion.

For Part D: After the primary database lock, please refer to the Schedule of Activities.

Parts A, B and C

If TnI is determined to be positive (TnI+) until the primary database lock, it will be re-tested by central laboratory within 3 days before permanent discontinuation of study treatment. A positive result from the TnI test means when the laboratory value exceeds the ULN as per each site or central laboratory range.

Part D

TnI is positive (TnI+) when the laboratory value exceeds the ULN as per local laboratory range and is clinically significant for a cardiac event. If TnI laboratory value exceeds the ULN, it will be re-tested by local laboratory within 3 days. If considered clinically significant, study treatment will be permanently discontinued after consultation with the Sponsor medical monitor. In Part D, central laboratory confirmation of TnI local laboratory value is not required.

Additionally a urine/serum sample will be collected from all females of child bearing potential at screening and discontinuation for a pregnancy test.

Cases where a patient shows an AST or ALT ≥3xULN or total bilirubin ≥2xULN need to be reported to the Sponsor within 24 hours. Prompt reporting of cases meeting Hy's law criteria (via the SAE expedited reporting system) is required for compliance with regulatory guidelines. The investigator is responsible for, without delay, determining whether a patient meets potential Hy's law criteria. The investigator needs to perform additional examinations for this and confirm the results with the Sponsor's Study Physician. Details of identification of potential Hy's Law cases and actions to take are detailed in Appendix A.

For blood volume see Section 6.6.1.

6.2.6. Other Safety Assessment

6.2.6.1. Ophthalmologic examination

Ophthalmic assessment, including slit lamp examination, fundoscopic examination, eye examination and other tests by investigator's judgement will be performed at screening and should be repeated if a patient experiences any visual symptoms (including blurring of vision), with additional tests if clinically indicated. Any clinically significant findings, including those confirmed by the ophthalmologist must be reported as an AE. Photographs should be performed to record any clinically significant findings. These photographs should be available for review by the Sponsor if necessary. Ophthalmology examination results should be collected in eCRF.

6.2.6.2. Echocardiography (or MUGA Scan)

Until the primary database lock, Echocardiography (or MUGA scan) to assess LVEF will be conducted at baseline (prior to first dose of YH25448), 12 weeks after the first dose of YH25448 and 12-weekly thereafter (± 1 week). Additional assessments can be conducted at the discretion of the investigator within every 12 weeks or during discontinuation visit. The modality of the cardiac function assessments must be consistent within a patient i.e. if echocardiography is used for the screening assessment then echocardiography should also be used for subsequent scans if required. The patients should also be examined using the same machine and operator whenever possible. Until the primary database lock, For any patient who

has at least one echocardiogram or MUGA that is considered abnormal by local assessment, the Sponsor collects all echocardiograms or MUGAs (obtained at Screening and all subsequent assessments) for the purpose of a central read.

6.2.6.3. Hepatitis screen, HIV screen

All patients will be screened for Hepatitis B surface antigen (HBsAg). Screening for Hepatitis C will be based on HCV antibodies. Additional hepatitis examination could be conducted if required.

Evaluation for HIV seropositivity will be performed, and, if positive, the further test can be determined as per investigator's decision if needed.

Appropriate counseling will be made available by the Investigator in the event of a positive finding. Notification of regional and/or national authorities, if required by law, will be the responsibility of the Investigator.

Results will be available as source data and will not be recorded within the eCRF.

6.2.6.4. Follow-up

A post study assessment will be performed at the time investigational product is permanently discontinued (see Table 8, Table 9, Table 10 and Table 11).

28 day follow-up should be made with the patient 28+ 7 days following the discontinuation of YH25448 to collect new AEs and follow up on any ongoing AEs and concomitant medications (including any subsequent cancer therapy). Refer to Section 7.3 for full details on AE recordings during follow-up.

Patients who discontinue YH25448 for reasons other than progression in expansion and extension phases will continue RECIST 1.1 assessments every 2 cycles (relative to first dose of multiple dosing) before subsequent anticancer therapy begins.

Patients with intracranial disease who are confirmed progression only in extracranial lesion will continue to perform RECIST 1.1 assessment every 2 cycles for intracranial lesion until progression if patients continuously administrate study drugs (for Parts A, B and C). 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.

AEs and SAEs should be collected until 28 days from the last day of dosing, and details of concomitant medications (including any subsequent cancer therapy) should continue to be collected as detailed in the study plan (see Table 8, Table 9, Table 10 and Table 11) up to the 28-day follow up visit. For those patients in expansion and extension phases an additional PRO QoL questionnaire should be completed on progression or discontinuation visit (Table 9 and

Table 10).

Only patient in dose extension, expansion phases and Part D (prior to Protocol Amendment 11) who is receiving treatment for selected dose after completing the 28-day follow-up visit will be followed for overall survival and subsequent anticancer therapy, via telephone contact, every 12 weeks until death, lost to follow-up or withdraws consent. As of Protocol Amendment 11, follow-up visits will not be required for patients in Part D; overall survival and subsequent anticancer therapy data will not be collected.

6.3. Pharmacokinetics

6.3.1. Collection of pharmacokinetic samples

Venous blood samples (approximately 9 mL for Parts A, B and C; 6 mL for Part D) for determination of concentrations of YH25448 and its potential metabolites, including M7, in plasma will be taken at the times presented in Table 13. The date and time of collection of each sample and the date and time of dose will be recorded. For patients in Part D, see also Table 12.

Table 13. PK blood sample schedule

Phase	Single dose	Multiple dose	
	Day 1, Cycle 0	Day 1, 8, 15, Cycle 1	Day 1, Cycle 2
Part A	Pre-dose (0 h), 0.5, 1, 2, 4, 6, 8, 10, 12, 24, 48, 60 hrs post-dose	Each pre-dose (0 h)	Pre-dose (0 h), 0.5, 1, 2, 4, 6, 8, 10, 12, 24 hrs post-dose
Part B	-	Each pre-dose (0 h)	Pre-dose (0 h), 0.5, 1, 2, 4, 6, 8, 10, 12, 24 hrs post-dose
Part C	-	Each pre-dose (0 h)	-
Part D*	Pre-dose (0 h), 1, 2, 4, 10, 24, 48 hrs post-dose	Each pre-dose (0 h)	Pre-dose (0 h), 1, 2, 4, 10, 24 hrs post-dose

* Additional blood samples will be taken on Day 1 in every other cycle from Cycle 3 onwards until the primary database lock.

For Parts A, B and C, a ±5 min window will be allowed for blood samples taken at 0.5, 1 h; a ±10 min window at 2-12 h; a ±1 h window at 24 h; a ±2 h window at 48, 60 h. A -2 h window will be allowed for samples taken at pre-dose in Day 1, Cycle 0 and Cycle 1; a -15 min window at pre-dose in Day 8 and Day 15, Cycle 1. The samples for pre-dose in each day should be taken prior to the administration of IP.

The timing of the pharmacokinetic samples may be adjusted during the study, dependent on emerging data, in order to ensure appropriate characterization of the plasma concentration-time profiles. The total number of samples and the total volume of blood taken from each patient

will not exceed that detailed in Section 6.6.1. Residual samples may be analyzed for exploratory biomarkers.

No PK blood samples will be taken following primary database lock.

Details of blood sample collection, handling, shipment, storage and processing for PK analysis of the plasma concentrations of YH25448 will be provided to the center in the laboratory manual.

6.3.2. Determination of drug concentration in pharmacokinetic samples

Concentrations of YH25448 and its potential metabolites, including M7, in plasma and CSF will be analyzed, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

All samples still within the known stability of the analyses of interest (i.e., YH25448 and its metabolite M7) at the time of receipt by the bioanalytical laboratory will be analyzed.

In addition, the pharmacokinetic samples may be subjected to further analyses by the Sponsor in order to investigate the presence and/or identity of additional drug metabolites. Any results from such analyses will be reported separately from the Clinical Study Report. Any residual plasma after PK analysis may be used for exploratory research into factors that may influence development of NSCLC and/or response to YH25448.

Details on sample processing, handling, shipment and storage are provided in the laboratory manual.

6.4. Exploratory Research

6.4.1. Exploratory biomarker research

If a patient agrees to participate in the exploratory biomarker research component of the study biological samples (e.g., plasma, serum, archived and study-obtained tumor, etc.) will be collected and may be analyzed for exploratory biomarkers to assess correlations with disease activity, effects of study drug and clinical outcomes.

The results of this exploratory biomarker research will be reported separately and will not form part of the Clinical Study Report.

The results of this exploratory biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future studies.

No samples will be taken for exploratory research following primary database lock

6.4.1.1. Collection of Tumor Samples

All patients will be asked to provide consent to supply a sample of their archival tumor blocks, T790M mutation must be centrally confirmed within 28 days before starting administration of YH25448 and a tissue sample must be collected after the progression disease on the therapy recently (except for Part D). During the screening, if there is a sample which is meet the conditions required above, an archived tissue sample is able to be used for T790M mutation confirmation (Only in part A, dose escalation phase, if an archive sample is collected after progression disease on authorized EGFR TKIs therapy regardless of the recent treatment, the sample is able to be used for T790M mutation confirmation). Any archival biopsy samples taken following previous lines of therapy will also be asked to provide consent to supply it, if available. In each case the previous patient treatment must be clearly indicated for each sample provided. For the 1st line treatment cohort of Part C dose extension phase, the tumor tissue sample collected prior to initiation of the study treatment should be submitted for central confirmation. The mutation test will be performed later. For the 2nd line treatment cohort of Part C, if the T790M mutation is confirmed locally, then the collected tumor tissue sample must be submitted for the central confirmation before the enrollment.

All patients (except for Part D) will be asked to consent to optional biopsies. These biopsy samples will be used to support the development of the diagnostic assay and further exploratory research.

The optional screening sample should be obtained at the same time and as part of the same sample procedure as the mandatory biopsy for T790M status.

Tumor samples will preferably be in the form of a formalin fixed paraffin embedded block (tissue derived from the diagnostic tumor or a metastatic site). If this is not possible, slides of freshly prepared unstained 5 micron sections from the archival tumor block may be provided.

Further details on sample processing, handling and shipment are provided in the laboratory manual.

6.4.1.2. Collection of exploratory Blood-born biomarker

Approximately 20 mL blood sample will be collected to provide plasma to evaluate genetic mutations including but not limited to EGFR mutations, which may be predictive of the activity of YH25448. But the volume of blood can be reduced by 10 mL considering patients' condition. For sampling schedule, see Study Plan (Table 8, Table 9 and Table 10).

Details of sample collection, processing, shipping and storage will be described in the laboratory manual.

6.4.1.3. Collection of plasma for exploratory analysis of cfDNA

All patients (except for Part D) will be requested to provide mandatory plasma samples for analysis of circulating free tumor DNA (cfDNA) until the primary database lock at screening and every 2 cycles until disease progression (as per RECIST 1.1). The sample may be used to further investigate the relationship between PK and blood-born biomarkers.

Approximately 20 mL blood sample will be collected to provide plasma but the volume of blood can be reduced by 10 mL considering patients' condition.

Plasma samples will be taken at the following times:

- Screening
- Pre-dose Day 1
- Every 2 cycles up to and including progression (corresponding with the RECIST 1.1 assessments)
- Discontinuation of treatment

The samples will be analyzed for a range of oncology biomarkers which may correlate with drug response.

Details on sample processing, handling, shipment and storage are provided in the laboratory manual.

6.4.1.4. Collection of cerebrospinal fluid

If the patient agrees, a sample of CSF (minimum 2 mL up to 5 mL) will be obtained at one time point taken at any time from Day 1 Cycle 2 onwards. Samples will be collected, labeled and stored and shipped as detailed in the laboratory manual.

Any residual CSF after PK analysis may be used for exploratory research into factors that may influence development of NSCLC and/or response to YH25448.

For Part D: No CSF samples will be collected

6.4.2. Collection of Pharmacogenetics samples

If a patient agrees to participate in the host pharmacogenetics research component of the study, a blood sample will be collected. The results of this pharmacogenetic research will be reported separately and will not form part of the Clinical Study Report.

In Parts A, B or C, the 10mL of blood sample for genetic research will be obtained from the patients immediately prior to the first administration of YH25448 in the study. In Part D the 10mL blood sample for assessment of genetic variants of GSTM1 may be collected at any time during the study although collection during screening is preferred. PK blood samples may also be utilized for this process. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event. Such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn prior to dosing, it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetics during the study. Samples will be collected, labeled, stored and shipped as detailed in the Laboratory Manual.

6.5. Patient Reported outcomes

The following PROs will be administered: EORTC QLQ C-30, QLQ-LC13 and QLQ-BN20 until the primary database lock.

EORTC QLQ-C30 and QIQ-LC 13 and QLQ-BN20

The EORTC QLQ-C30 was developed by the EORTC Quality of Life Group 1993. It consists of 30 items and measures cancer patients' functioning (HRQoL) and symptoms[10]. The EORTC QLQ-BN20 (BrM patients only) was developed for use among brain cancer patients varying in disease stage and treatment modality (i.e. surgery, chemotherapy, radiotherapy, etc.). It should always be complemented by the QLQ-C30[11]. Relevant symptom questions from QLQ-BN20 will be used to explore CNS symptom improvement. The QLQ-LC13 is a complementary module measuring lung cancer associated symptoms and side-effects from conventional chemotherapy and radiotherapy.[12]

Administration of PROs

Questionnaires will be administered using paper questionnaires. The patient should complete the questionnaires at the scheduled clinic visit at screening, every 2 cycles relative to the first dose of multiple dosing and progression as specified in the study plan (Table 8, Table 9 and Table 10).The patient should also complete a questionnaire progression. If any scheduled PRO assessment is not completed, the reason for non-completion should be recorded.

PROs will be filled out prior to any other center activities when patient visit the center. The patients will be instructed to complete the PRO independently. This center will have a designated quiet space for patients to use when completing the assessments. Each center should allocate responsibility for PRO assessment to a specified individual (e.g. a research nurse). It is important that the value and relevance of HRQoL data are explained carefully to participating patients so that they are motivated to comply with data collection. The research nurse or appointed individual should also stress that the information is confidential. Therefore, if the

patient has any medical problems he/she should discuss them with the doctor or research nurse separately from their HRQoL assessment.

The instructions for completion of questionnaires are:

- It must be completed before any investigations or discussions about the status of the patient's disease with the clinic staff.
- The patient must complete it themselves without any intervention from family, friends, centre staff etc.
- The only exception to this is if the patient is blind or illiterate. In this case the questionnaire may be read to the patient verbatim, however the reader must not aid in the interpretation of questions or in the selection of answers.
- Only one answer to every question should be checked.
- Centre personnel should not review the responses to the questionnaire with the patient or with any other centre staff.

Following completion, the research nurse or appointed individual may quickly scan the questionnaire visually for completeness and should confirm verbally with the patient that the questionnaire has been completed fully.

6.6. Biological sampling procedures

6.6.1. Volume of blood

The number of samples taken, as well as the volume required for each analysis, may be changed during the study as new data on YH25448 become available. The estimated total volume of blood that will be drawn from each patient in this study for mandatory and optional samples, see Table 14.

Safety laboratory assessments will be performed locally at each center's laboratory by means of their established methods. The number of samples/blood volumes is therefore patient to site-specific change.

Table 14. Blood Volume

Assessment					
Visit	**Blood Biomarker & Pharmacogenetic Testing[3]**	**cfDNA (except for Part D)**	**Safety (hematology and chemistry)**	**PK for Parts A, B and C[2]**	**PK for Part D[4]**
Screening	(20 mL[1]+10mL)	20mL	15mL	-	
Day 1, Cycle 0	-	20mL	15mL	81 mL (9 mL x	30 mL (6 mL x

		every 2 cycles corresponding to RECIST 1.1 tumor assessment[1]		9)	5)
Day 2, Cycle 0	-		-	9 mL	6 mL
Day 3, Cycle 0	-		15mL	18 mL(9 mL x 2)	6 mL
Day 1, Cycle 1	-		15mL	9 mL	6 mL
Day 8, Cycle 1	-		-	9 mL	6 mL
Day 15, Cycle 1	-		15mL	9 mL	6 mL
Day 1~2, Cycle 2 and every 2 cycles	-		15mL	Cycle 2, Day 1: 81 mL (9 mL x 9) Cycle 2, Day 2: 9 mL	Cycle 2, Day 1: 30 mL (6 mL x 5) Cycle 2, Day 2: 6 mL Every other cycle from Cycle 3 onwards, Day 1: 6mL
Unscheduled visit	-		(15mL)	-	
Discontinuation	-		15mL	-	

1. The volume of blood for blood biomarker and cfDNA can be reduced by 10 mL considering patient's condition (for Parts A, B and C only).
2. Cycle 0 for Part A; Cycle 1 for Parts A, B and C; Cycle 2 for Parts A and B; About 9 ml blood sample will be collected at a time.
3. It is optional samples
4. About 6 ml blood sample will be collected at a time for Part D.

6.6.2. Handling, storage and destruction of biological samples

The samples will be used up, or disposed of after analyses or retained for further use as described below.

Any PK sample remaining after analysis for YH25448 and its potential metabolites, including M7, may be used for exploratory biomarker analyses. These analyses are for Sponsor use only and will not be included in the Clinical Study Report.

Biological samples for future research will be retained at the Sponsor or its designee for a maximum of 15 years following the finalization of the Clinical Study Report. The results from future analysis will not be reported in the Clinical Study Report but separately in a bioanalytical method validation report.

6.6.3. Pharmacokinetic samples

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples and reported in a separate bioanalytical report.

Key samples for metabolite identification and/or analysis will be retained at designated contract

laboratory, on behalf of the Sponsor for a maximum of 5 years following the finalization of the Clinical Study Report. The results from the investigation will not be reported in the Clinical Study Report but separately report.

6.6.4. Samples for exploratory research

Details of sample collection, processing, shipping and storage will be described in the laboratory manual.

Each sample for exploratory research will be identified with the study number and patient enrolment number. In this way exploratory biomarker and genetic data may be correlated with clinical data, samples destroyed in the case of withdrawal of consent and regulatory audit enabled.

Where genetic analysis will be undertaken the processes adopted for the coding and storage of samples will be more stringent in order to maintain patient confidentiality. As an added precaution, irrespective of the type of sample, the DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number will be used to identify the sample and corresponding data at the Sponsor, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (Sponsor employee or contract laboratory staff) working with the DNA.

The samples and data for genetic analysis in this study will be single coded. The link between the patient enrolment code and the DNA number will be maintained and stored in a secure environment, with restricted access at the Sponsor, or at the designated contract laboratory. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent when the patient has requested disposal/destruction of collected samples not yet analyzed.

6.6.5. Labeling and shipment of biohazard samples

The Principal Investigator ensures that samples are labeled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see appendix C of this Clinical Study Protocol ‘IATA 6.2 Guidance Document’.

Any samples identified as infectious category A materials are not shipped and no further samples taken from the patient unless agreed with the Sponsor and appropriate labeling, shipment and containment provisions are approved.

All archival tumor samples should be shipped at ambient temperature as per the laboratory

manual to the Sponsor designated central Contract Research Organization.

6.6.6. Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator at each center keeps full traceability of collected biological samples from the patients while in storage at the center until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

The sponsor keeps oversight of the entire life cycle through internal procedures, monitoring of study centers and auditing of external laboratory providers.

Samples retained for further use are registered in the Sponsor or the designated contract laboratory during the entire life cycle.

6.6.7. Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of voluntarily donated biological samples, then the samples will be disposed of/destroyed, and the action documented. If samples are already analyzed, the Sponsor is not obliged to destroy the results of this research. The patient may continue in the study.

The Principal Investigator:

- Ensures the Sponsor is notified immediately of the patient's withdrawal of informed consent to the use of donated biological samples
- Ensures that biological samples from that patient, if stored at the study centre, are immediately identified, disposed of/destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study centre

6.7. Anti-tumor activity

6.7.1. Tumor assessments

RECIST 1.1 guidelines for measurable, non-measurable, target lesions (TLs) and non-target lesions (NTLs) and the objective tumor response criteria are presented in appendix F of this Clinical Study Protocol. Baseline CT or MRI assessments of chest and abdomen (including

liver and adrenal glands) must be performed no more than 28 days before the start of study treatment, and ideally should be performed as close as possible to the start of study treatment. Additional imaging may be performed based on individual patient signs and symptoms MRI (or CT if not applied to MRI) scan of the brain should be performed in all patients. In Part D (patients outside Korea) a brain MRI will be performed at screening in all patients. The methods of assessment used at baseline should be used at each subsequent follow-up assessment. Follow-up assessments should be performed every 2 cycles (± 7 days) after the start of multiple dosing until objective disease progression as defined by RECIST 1.1 even if a patient discontinues treatment prior to progression. 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. Responses and disease progression status will be recorded in EDC.

Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment is performed and the patient has not progressed, every attempt should be made to perform subsequent assessments at the scheduled visits whilst the patient remains on study treatment.

Categorization of objective tumor response assessment will be based on the RECIST 1.1 guidelines for response: CR (complete response), PR (partial response), SD (stable disease) and PD (progression of disease). Target lesion progression will be calculated in comparison to when the tumor burden was at a minimum (i.e. smallest sum of diameters previously recorded on study). In the absence of progression, tumor response (CR, PR, SD) will be calculated in comparison to the baseline tumor measurements obtained before starting treatment.

If the investigator is in doubt as to whether progression has occurred, particularly with response to NTLs or the appearance of a new lesion, it is advisable to continue treatment and reassess the patient's status at the next scheduled assessment or sooner if clinically indicated. If repeated scans confirm progression, then the date of the initial scan should be declared as the date of progression.

To achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal disease progression status.

The RECIST 1.1 guidelines for measurable, non-measurable, target and non-target lesions and the objective tumor response criteria (complete response, partial response, stable disease or progression of disease) will be modified for the separate assessment of extracranial disease and intracranial disease in brain metastatic patients according to Appendix F.

Intracranial disease will be assessed separately from extracranial disease using RECIST 1.1

criteria and appendix F and a separate assessment of CR (complete response), PR (partial response), SD (stable disease) and PD (progression of disease). Target lesion (TL) progression will be calculated in comparison to when the tumor burden was at a minimum (i.e. smallest sum of diameters previously recorded on study). In the absence of progression, tumor response (CR, PR, SD) will be calculated in comparison to the baseline tumor measurements obtained before starting treatment.

If study treatment continues after the patient experiences disease progression extracranially but with improved/stable intracranial disease, the patient should continue RECIST 1.1 assessments based on appendix F every 2 cycles until disease progression intracranially (for Parts A, B and C only) 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. Responses and disease progression status will be recorded in EDC.

Table 15. Radiological assessment follow-up according to the response

Extracranial Response	Intracranial Response	Overall response	Radiological Assessment Follow-up
Non-PD or NE	Non-PD or NE	Non-PD or NE	Continue radiological assessments until disease progression
PD	Non-PD or NE	PD	Continue radiological assessments until disease progression intracranially
Non-PD or NE	PD	PD	Discontinue radiological assessment
PD	PD	PD	Discontinue radiological assessment

Non-PD: complete response, partial response, stable disease
PD: progressive disease
NE: Not evaluable

It is important to follow the assessment schedule as closely as possible. Please refer to the study plan in Section 6.1 and appendix F.

All RECIST 1.1 assessment images will be reviewed centrally (for Parts A, B and C only). Duplicates may be collected and stored by the Sponsor appointed representative, and sent for independent central review, if deemed appropriate.

The independent central review will be performed for all patients (for Parts A, B and C only). Details of the independent central review will be documented in the Independent Review Charter.

After the primary database lock, the independent central review will not be performed anymore.

7. ADVERSE EVENTS

The principal investigator is responsible for ensuring that all staff involved in the study is

familiar with the content of this section.

7.1. Definitions of 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. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

Any deterioration of the disease under study and associated symptoms or findings should not be regarded as an adverse event as far as the deterioration can be anticipated (see Section 7.3.7).

The term adverse event is used generally to include any AE whether serious or non-serious.

7.2. Definition of Serious Adverse Events

A serious adverse event (SAE) is an AE occurring during any study phase (i.e., run-in, treatment, washout and follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is life-threatening (defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires in patient hospitalization or causes prolongation of existing hospitalization (see note below for exceptions)
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is or results in a congenital abnormality or birth defect
- Any important medical event such as the occurrence of drug dependence or abuse or blood disorders. (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)

All pregnancies, regardless of outcome, must be reported to the Sponsor on a Pregnancy Surveillance Form. Although cancer is not always serious by regulatory definition, these events should be reported to the Sponsor in an expedited manner according as SAEs.

NOTE:

The following hospitalizations are not considered SAEs in Sponsor clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an "important medical event" or event life threatening)
- elective surgery, planned prior to signing consent
- admissions as per the protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- medical/surgical admission for purposes other than remedying ill health state and that are planned prior to entry into the study. Appropriate documentation is required in these cases
- admission due to another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative)

7.3. Recording of adverse events

7.3.1. Time period for collection of adverse events

AEs will be collected throughout the study, from informed consent until the end of the follow-up period. The follow-up period is defined as 28 days after study treatment is discontinued. SAEs occurring in the 28 follow-up period should be reported to the Sponsor in the usual manner (see Section 7.4).

Following discontinuation of YH25448, SAEs considered related to study procedures should continue to be collected.

After the primary database lock, there may be some patients remaining on study treatment. For these patients who are continuing to receive YH25448, the Sponsor will collect information (during the treatment period and for 28 days after last dose) on SAEs, deaths (including those due to disease progression), discontinuation due to AEs/SAEs and drug accountability only.

7.3.2. Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the CRF. The Sponsor retains the right to request additional information for any patient with ongoing AE(s) at the end of the study, if judged necessary.

If an investigator learns of any SAEs, including death, at any time after a patient has completed the study and he/she considers there is a reasonable possibility that the event is related to YH25448, the investigator should notify the Sponsor.

7.3.3. Variables

The following variables will be collected for each AE:

- AE diagnosis/description
- The date when the AE started and stopped
- CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the investigational product (yes or no) (Certain, Probable/Likely, Possible, Unassessable/Unclassifiable will be considered to 'Yes' and Unlikely, Not related will be considered to 'No'.)
- Action taken with regard to investigational product
- Outcome

For SAEs other variables will be collected including treatment given for the event.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity, an AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE. Seriousness is defined by the criteria in Section 7.2.

The grading scales found in the National Cancer Institute CTCAE 4.03 version will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used. A copy of the CTCAE version can be

downloaded from the Cancer Therapy Evaluation Programmed website (https://ctep.cancer.gov/).

7.3.4. Causality collection

The investigator will assess causal relationship between investigational product and each adverse event, and answer 'yes (Certain, Probable/Likely, Possible, Unassessable/Unclassifiable)' or 'no (Unlikely, Not related)' to the question: 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs causal relationship will also be assessed for other medication and study procedure. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

7.3.5. Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or care provider or reported in response to the open question from the study personnel: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

7.3.6. Adverse events based on examinations and tests

The results from protocol mandated laboratory tests, vital signs, ECGs and other safety assessments will be summarized in the Clinical Study Report. Deterioration as compared to baseline in these parameters will therefore only be reported as AEs if they fulfill any of the criteria for a SAE, a DLT or are the reason for discontinuation of treatment with the investigational product unless clearly due to progression of disease under study (see Disease progression as below).

If deterioration in a laboratory value, vital sign, ECG or other safety assessment is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or other finding will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (e.g., anemia versus low hemoglobin value). In the absence of clinical signs and symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value that is unequivocally due to disease progression should not be reported as an AE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

7.3.7. Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events that are unequivocally due to disease progression should not be reported as AEs during the study.

7.3.8. New cancers

New cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the patient's inclusion in this study. They do not include metastases of the original cancer. The development of a new cancer should be regarded as an AE and should be reported according as the AE.

7.3.9. Handling of deaths

All deaths that occur during the study, or within the follow-up period after the administration of the last dose of investigational product, should be reported as follows:

- Death, which is unequivocally due to disease progression, should be communicated to the study monitor at the next monitoring visit and should be documented in the CRF module, but should not be reported as a SAE during the study
- Where death is not clearly due to disease progression of the disease under study the AE causing the death should be reported to the study monitor as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign a single primary cause of death together with any contributory causes
- Deaths with an unknown cause should always be reported as a SAE but every effort should be made to establish a cause of death. A post-mortem may be helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results (with translation of important parts into English) should be reported in an expedited fashion to a Sponsor representative within the usual timeframes

7.4. Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product or to the study procedure(s) and will be recorded in the eCRF.

If any SAE occurs in the course of the study, then investigators or other center personnel inform appropriate Sponsor representatives immediately, or no later than 24 hours of when he or she becomes aware of it.

The designated Sponsor representative works with the investigator to ensure that all the necessary information is provided to pharmacovigilance department within one calendar day of initial receipt for fatal and life threatening events and all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other center personnel inform the Sponsor representatives of any follow-up information on a previously reported SAE immediately, or no later than 24 hours of when he/ she becomes aware of it.

Once the investigators or other center personnel indicate an AE is serious, then the investigator or other study center personnel reports a SAE to the appropriate Sponsor representative. The Sponsor representative will advise the investigator/study center personnel how to proceed.

7.5. Contact Information for reporting SAE

SAE EMAIL TRANSMISSION: PPD

SAE CONTACT

COUNTRY	Toll Free Fax-No	Toll Free Phone-No
SOUTH KOREA	PPD	PPD
OUTSIDE KOREA	PPD	PPD

SAE Alternative CONTACT

SOUTH KOREA: P
OUTSIDE KOREA: PPD

7.6. Overdose

There are no data on overdosing is available since this is the first study in humans with YH25448. There is no definition of what constitutes an overdose and no known antidote. Except the case of the dose escalation, investigators will be advised that any patient who receives a higher dose than that intended daily dose should be monitored closely, managed with appropriate supportive care and followed up expectantly.

Such overdoses should be recorded as follows:

- An overdose with associated AEs/SAEs is recorded as the AE diagnosis/symptoms on the relevant AE/SAE modules in the eCRF and on the overdose eCRF module.

- An overdose with no associated symptoms is only reported on the overdose eCRF module.

If an overdose with associated AEs/SAEs occurs in the course of the study, then investigators or site staff inform the Sponsor representatives immediately a completed Report within 24 hours of knowledge of the event.

The designated Sponsor representative works with the investigator to ensure that all relevant information is provided to the eCRF.

For overdoses associated with a SAE, standard reporting timelines apply, see Section 7.4.

7.7. Pregnancy

All pregnancies and their subsequent outcome (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be reported to the Sponsor using the appropriate forms during the course of the study and within 28 days of the last dose of YH25448.

7.7.1. Maternal exposure

If a patient becomes pregnant during the course of the study investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of a pregnancy should be followed up and documented even if the patient was withdrawn from the study but not more than 30 days after completion of the pregnancy.

If a pregnancy occurs during exposure to investigational product or in the 28 days after discontinuing investigational product, then investigators or other center personnel inform the Sponsor representatives immediately by faxing or emailing a completed Pregnancy Report within 24 hours of knowledge of the event.

The same timelines apply when outcome information is available.

7.7.2. Paternal exposure

Pregnancy of a patient's partner is not considered to be an adverse event.

However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented.

To capture information about a pregnancy from the partner of a male patient, the male patient's partner consent must be obtained to collect information related to the pregnancy and outcome. A consent form specific to this situation must be used. The outcome of any conception occurring from the date of the first dose until 3 months after dosing ends should be followed up and documented.

7.7.3. Requirements for Pregnancy Testing

All WOCBP MUST have a negative pregnancy test result at screening prior to receiving the investigational product and discontinuation visit (refer to inclusion criterion 2 in section 4.2.1). If the pregnancy test result is positive, the patient must not receive the investigational product and must not continue in the study.

Pregnancy testing must also be performed throughout the study as specified in Section 6.1 (see flow chart/time and events schedule) and the results of all pregnancy tests (positive or negative) recorded on eCRF.

In addition, all WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

7.7.4. Reporting of Pregnancy

If, following administration of the investigational product, it is subsequently discovered that a study patient is pregnant or may have been pregnant, the investigator must immediately notify the Sponsor representative of this event, record the pregnancy on the Pregnancy Surveillance Form (not an SAE form) within 24 hours. Initial information on a pregnancy must be reported immediately to the Sponsor and the outcome information provided once the outcome is known. Completed Pregnancy Surveillance Forms must be forwarded to the Sponsor in accordance with SAE reporting procedures described in Section 7.4.

Protocol-required procedures for study discontinuation and follow-up must be performed with the patient unless contraindicated by pregnancy (e.g., X-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. Follow-up information regarding the course of the pregnancy, including prenatal and neonatal outcome must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to the Sponsor study physician. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

8. STATISTICAL CONSIDERATIONS

8.1. Sample Size Determination

Part A: Dose Escalation Phase

Approximately 30 patients with EGFRm+ NSCLC who had progressed following prior EGFR TKIs therapy will be enrolled in dose escalation phase. The total number of patients will depend upon the number of dose escalations necessary. At least 3 and up to 6 evaluable patients will be required for each dose cohort.

Part B: Dose Expansion Phase

Approximately 20 evaluable patients with T790M+ mutation NSCLC, on the basis of central confirmed T790M mutation result, regardless of asymptomatic brain metastasis or without brain metastasis (2nd line expansion with/without BrM) who had progressed following prior EGFR TKIs therapy will be enrolled per dose cohort. There are no specific stopping criteria for this phase of the study, however, emerging data from expansion phases will be monitored regularly and decided to stop patients enrollment by the SRC.

Part C: Dose Extension Phase

2nd line therapy cohort

A total of 60 evaluable patients is required for the 2nd line therapy cohort in Part C. This sample size will provide 88% power to test a difference of 45% (not considered clinically compelling) versus 65% (ORR of minimal clinically meaningful) using a one-sided 0.025 alpha level[13].

An example of ORR and the corresponding 95% confidence interval is provided below:

- 40% ORR (24/60 responses); 95% CI [27.6%, 52.4%]
- 50% ORR (30/60 responses); 95% CI [37.3%, 62.7%]
- 60% ORR (36/60 responses); 95% CI [47.6%, 72.4%]
- 70% ORR (42/60 responses); 95% CI [58.4%, 81.6%]
- 80% ORR (48/60 responses); 95% CI [69.9%, 90.1%]

1st line therapy cohort

A total of 40 evaluable patients is required for the 1st line therapy cohort in Part C. This sample size will provide 93% power to test a difference of 55% (not considered clinically compelling) versus 80% using a one-sided 0.025 alpha level[14, 15].

An example of ORR and the corresponding 95% confidence intervals is provided below:

- 50% ORR (20/40 responses); 95% CI [34.5%, 65.5%]
- 60% ORR (24/40 responses); 95% CI [44.8%, 75.2%]
- 70% ORR (28/40 responses); 95% CI [55.8%, 84.2%]
- 80% ORR (32/40 responses); 95% CI [67.6%, 92.4%]
- 90% ORR (36/40 responses); 95% CI [80.7%, 99.3%]

Part D: Patients Outside Korea

Approximately 12-15 patients outside Korea will be enrolled at each 240 mg and 320 mg dose level to provide a minimum of 6 Caucasian patients with evaluable PK. Although enrollment will not be based on race, it is expected that approximately 80% of patients will be Caucasian. All patients will have progressed following prior EGFR TKI therapy.

8.2. Populations for Analyses

The analyses of data will be based on different populations according to the purpose of the analyses. Throughout the safety results sections, erroneously treated patients (e.g., those assigned to receive dose A mg who actually received dose B mg, those who failed to meet the selection criteria) will be accounted for in the actual dose group received. Analysis populations are described below:

- Screened population: all patients who have signed a written ICF and received a screening number
- Safety analysis population: All patients who received at least one dose of IP
- Evaluable for response population: All patients in the safety analysis population who has a baseline RECIST 1.1 assessment whose tumor EGFR 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).
- Brain metastatic full analysis population: All patients in the evaluable for response population who have a measurable and/or unmeasurable intracranial lesion at baseline.
- 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.
- Pharmacokinetic analysis population: All patients who have at least one measurable concentration collected post-dose.
- Exploratory biomarkers analysis population: All patients that participate in the exploratory biomarker research.

8.3. Patient Disposition

The number of patients in the safety, evaluable for response, pharmacokinetic populations will be summarized by dose level, overall, and by institute. The screened population will only be summarized overall and by study center. Screening failures (i.e., patients who signed the ICF but are not received at least one dose of IP) and the associated reasons for failure will be tabulated overall.

All enrolled patients will be accounted for in the patient disposition table. The number of patients and percentage of patients will be presented for discontinued patients, and for each reason for discontinuation. Reasons for discontinuation of investigational product will be listed including the study day of treatment discontinuation and will be summarized by dose group.

Important deviations from protocol will be summarized and listed for all patients.

8.4. Demographics and Other Baseline Characteristics

Demographic, baseline characteristics, extent of disease, ECOG performance status and smoking status of the patients will be listed for each patient and summarized by dose group.

Baseline information (e.g. medical and surgical history), prior chemotherapy, prior radiotherapy and concomitant medications (baseline and post first dose) will also be listed individually for each patient and summarized by dose group.

No statistical tests will be performed.

8.5. Assessment of Treatment Compliance

Exposure to investigational product i.e., total amount of study drug received will be listed for all patients.

Total exposure and total time on study (date of last dose minus date of first dose) will be summarized by the following: mean, standard deviation, minimum, maximum, median and number of observations. In addition, the number and percentage of patients with at least one dose interruption/dose delay and at least one dose reduction will be presented separately for the initial period defined as 21 days of multiple dosing (Cycle 1) and for any time following this initial period of the study.

8.6. Endpoint Definition

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. Safety analysis will be performed using the safety analysis population. PK analysis will be

performed using the pharmacokinetic analysis population. Unless specified otherwise, baseline for efficacy parameters is defined as the last non-missing efficacy measurement before the first administration of IP.

8.6.1. Efficacy Endpoints

8.6.1.1. Primary Endpoints (Parts A, B, and C)

- Safety and tolerability (primary for dose escalation and expansion phase)
- Objective response rate (ORR) (primary for dose extension, secondary for dose escalation and expansion phase)

8.6.1.2. Secondary Endpoints (Parts A, B, and C)

- PK parameters of YH25448 and its metabolites following a single oral dose and multiple oral doses.
- Duration of Response (DoR), disease control rate (DCR), tumor shrinkage
- Progression free survival (PFS) (secondary for dose expansion and extension phases)
- Overall survival (OS) (secondary for the selected extension dose in extension phase and extension phase)
    - For the BrM patients only (secondary for dose expansion and extension phases): objective intracranial response rate (OIRR), duration of intracranial response (DoIR), intracranial progression free survival (IPFS)

8.6.1.3. Primary and Secondary Efficacy Endpoints for Part D

Primary Endpoints

- Safety, tolerability, and PK of YH25448

Secondary Endpoints

- PK profiles of potential YH25448 metabolites in plasma, including M7, following a single oral dose and at steady state.
- Overall response rate (ORR)
- Duration of response (DoR)
- Disease control rate (DCR)

- Tumor shrinkage
- Progression free survival (PFS)
- Overall survival (OS)

8.6.2. Safety Variables

AEs, physical examination, clinical laboratory information, vital signs, ECOG performance status, ECG parameters, and concomitant medications/procedures will be tabulated and summarized.

8.6.3. Pharmacokinetic Endpoints

For each patient, the following PK parameters will be calculated, whenever possible, based on the plasma and CSF concentrations of YH25448 and its potential metabolites, including M6 and M7:

Following the single dose in Parts A and D:

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) of YH25448 and its metabolites, and apparent plasma clearance (CL/F), apparent volume of distribution (Vd/F) of YH25448, metabolic ratio (MR) of metabolites.

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

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}) of YH25448 and its metabolites, and apparent plasma clearance at steady state (CL_{ss}/F) of YH25448, metabolic ratio at steady state (MR_{ss}) of metabolites.

If sufficient data are available, population pharmacokinetic analysis of plasma concentration-time data of YH25448 may be performed using nonlinear mixed-effects modeling and will be reported in a separate report.

Following the multiple doses in Parts A, B and C:

CSF concentration (C_{CSF}) of YH25448 and its metabolites.

Following the multiple doses in all four Parts:

Trough plasma concentrations on Days 1, 8, 15 of Cycle 1 (C_{D1}, C_{D8}, C_{D15}).

8.6.4. Exploratory Endpoints

Parts A, B, and C

- Patient Reported Outcome: EORTC QLQ LC-13, QLQ C-30, QLQ BN-20 (Brain metastasis patients only)
- Metabolite identification
- Biomarker data
- Pharmacogenetics
- Diagnostic tumor samples

Part D

- Pharmacogenetic assessment of variants that encode GSTM1

8.7. Analyses

A detailed statistical analysis plan (SAP) will be completed prior to the final database lock. It will include details on the methodology used in the statistical analyses as well as details regarding reporting and data derivations.

With the exception of some safety and PK summaries that may be combined, data from the dose escalation and the dose expansion cohorts will be presented separately. PK summaries of Part D will be presented separately. All summaries will present data by dose group. Data from the extension cohort will always be presented separately. Pooled analysis as deemed appropriate will be defined in the SAP.

The data may be assessed to determine RD. At the completion of cycle 2 of the last patient in Part B, cycle 4 of the last patient in Part C 1st line, and cycle 6 of the last patient in Part C 2nd line, the database freeze will be performed for analysis. After appropriate follow-up to assess key endpoints, the primary database lock will be performed and will be reported in a CSR

After, the final database is locked to assess overall survival and safety, the relevant information may be provided separately from CSR.

The intent of all efficacy analyses from the expansion and extension phase is that it be focused on the population whose tumor EGFR mutation status is identified via central testing. Patients central test results must match the cohort to which they were assigned (i.e. T790M+ in the expansion phase).

8.7.1. Calculation or Derivation of Variables

8.7.1.1. Tumor Response Variables

For the investigator's assessment, at each visit patients will be assigned a RECIST visit response of CR, PR, SD or PD depending on the status of their disease compared to baseline and previous assessments.

Progression of TLs will be calculated in comparison to when the tumor burden was at a minimum (i.e., smallest sum of diameters previously recorded on study). In the absence of progression, tumor response (CR, PR, SD) will be calculated in comparison to the baseline tumor measurements obtained before starting treatment.

If a patient has had a tumor assessment, which cannot be evaluated, then the patient will be assigned a visit response of not evaluable (NE) unless there is evidence of progression in which case the response will be assigned as PD.

A visit response of CR will not be allowed if any of the TL data is missing.

For endpoints assessed by independent central review (ICR), review of all radiological imaging data will be carried out using RECIST version 1.1 and appendix F.

For brain metastatic patients, at each visit all patients will be assigned a appendix F extracranial visit response depending on the status of their disease compared with baseline and previous visit assessments. In addition, patients with intracranial disease will be assigned an intracranial visit response.

Overall visit response will be derived as from the extracranial time-point response and intracranial time-point response (Appendix F).

Overall tumor response and intracranial response by appendix F will be reported for BrM patients.

The following tumor response variables will then be derived:

- Overall tumor response in brain metastatic patients
  - Best objective response/objective response rate/disease control rate
  - Duration of response
  - Progression free survival

- Intracranial disease in brain metastatic patients
  - Intracranial best objective response/objective response rate/disease control rate
  - Duration of intracranial response
  - Week 6 and week 12 percentage change in tumor size
  - Intracranial progression free survival

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-PD, the patient's BOR will be grouped with the SD category. Individual target, non-target and new lesion assessments, as well as tumor response by visit, by ICR and investigator, will be listed.

8.7.1.2. Pharmacokinetic Variables

C_{max}, $C_{max,ss}$, T_{max}, $T_{max,ss}$, C_{D1}, C_{D8}, C_{D15} and C_{CSF} will be determined by visual inspections of the concentration-time profiles. AUC_t, $AUC_{0\ 24}$ and AUC_{ss} will be calculated using the linear trapezoidal rule. Where appropriate, AUC_{inf} will be extrapolated to infinity using the formula AUC_{inf} AUC_t+C_t/λ_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 $\ln 2/\lambda_z$. 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 $AUC_{ss}/AUC_{0\ 24}$.

The PK parameters will be calculated, if appropriate, using commercial software such as WinNonlin (Pharsight Corporation, Version 6.4 or higher). The actual sampling times will be used in the PK parameter calculations, and the PK parameters will be derived using noncompartmental methods. Other data handling procedures will be detailed in the SAP.

8.7.2. Efficacy Analyses

8.7.2.1. Primary Analyses

Part A and Part B: Dose Escalation and Dose Expansion Phase and Part D

Safety and tolerability will be assessed in terms of AEs, physical examination, laboratory data, vital signs and ECG assessments. All patients who receive at least one dose of YH25448 will

be included in the assessment of the safety profile (safety analysis population). These safety measures will be listed and summarized descriptively in the safety analysis population, as appropriate.

Part C: Dose Extension Phase

Objective Response Rate (ORR)

Objective response rate (ORR) is defined as the percentage of patients who have at least one confirmed partial or complete response (PR or CR) (according to RECIST 1.1 or appendix F) prior to disease progression or recurrence.

A visit response of CR is defined when all target lesions (TLs) and non-target lesions (NTLs) present at baseline have disappeared (with the exception of lymph nodes which must be <10mm to be considered non-pathological) and no new lesions have developed since baseline. A visit response of PR is defined when the sum of diameters of the TLs has decreased by 30% or more compared to baseline (with no evidence of progression) and the NTLs are at least stable with no evidence of new lesions. A confirmed response of PR or CR means that a response of PR or CR is recorded at one visit and confirmed by repeat imaging at least 4 weeks later with no evidence of progression between confirmation visits.

In the case of stable disease, measurements should have met the stable disease criteria for a minimum interval of 5 weeks (6 weeks minus the 7-day visit window) following the start of treatment.

The analysis population for objective tumor response rate will be the “evaluable for response” population.

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. However, any complete response or partial response which occurred after a further anticancer therapy was received will not be included in numerator of the ORR calculation. ORR will be presented with two-sided 95% confidence intervals using the normal approximation.

Analyses will be performed for assessments by ICR as well as by investigator, but the primary analysis for ORR will be based on ICR.

8.7.2.2. Secondary Analyses

Duration of Response (DoR)

Duration of response (DoR) is defined as the time from the date of first documented responses

(that is subsequently confirmed) until date of documented progression or death (same as PFS event time) whichever comes first. The time of the initial 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.

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

Progression Free Survival (PFS)

PFS is defined as the time from first dosing date until documented disease progression or death from any cause whichever first based on ICR as well as investigator assessment using RECIST 1.1 or appendix F. Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. In general, the PFS censoring rules and definition of progression date follow the Food and Drug Administration (FDA) “Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007)”.

If the patient progresses or dies after two or more missed visits, the patient will be censored at the time of the latest evaluable RECIST 1.1 assessment. If the patient has no evaluable visits or does not have baseline data they will be censored at day 0 unless they die within two visits of baseline. Two missed tumor assessment visit is defined as no assessment within 14 weeks (98 days) of start of treatment or the previous evaluable RECIST 1.1 measurement.

If a patient discontinues treatment prior to progression and/or receives a subsequent therapy prior to progression then these patients will continue to be followed until evidence of objective disease progression as defined by RECIST 1.1.

Table 16. The definition of outcome

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)	Progressed
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	Progressed
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 for the expansion and extension phases. PFS will be summarized for the expansion and extension phases. PFS will be displayed using Kaplan-Meier plot. The number of events, median (calculated from the Kaplan-Meier plot), and proportion of patients without an event at 6, 12, and 18 months will be summarized.

Disease Control Rate (DCR)

DCR is defined as the proportion of patients with a best overall, extracranial and intracranial response of CR, PR or SD.

In the case of stable disease, assessments should have met the stable disease criteria for at least 5 weeks after the study start.

Two-sided 95% confidence intervals DCR will be calculated using asymptotic normal approximation by dose level and total.

Tumor Shrinkage (Change in Tumor Size)

Tumor size is defined as the sum of the lengths of the longest diameters of the RECIST 1.1 or appendix F target lesions. 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.

The best change in tumor 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. Missing target lesion data at visits may be imputed using appropriate imputation rules.

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

The analysis population for change in tumor size will be the evaluable for response population.

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 may be produced, if appropriate, depending on how much data is obtained in patients with measurable disease at baseline. If there is only limited data then percentage change in tumor size will be listed only.

Objective Intracranial Response Rate (OIRR)

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

The OIRR will be analyzed by the brain metastatic full analysis population and brain metastatic evaluable for response population.

OIRR will be presented with two-sided 95% confidence intervals (Clopper-Pearson interval) by dose level and total.

Duration of Intracranial Response (DoIR)

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 (same as intracranial PFS event time according to appendix F) whichever comes first in brain metastatic patients. 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.

DoIR will be analyzed by brain metastatic evaluable for response population. DoIR in intracranial responding patients will be summarized and the number of responding patients with a duration of response (>3; >6; >9; >12 months) will be presented in brain metastatic

patients. A Kaplan-Meier plot and median DoIR with 95% CI (calculated from the Kaplan-Meier plot) will be presented by dose level and total.

Intracranial Progression Free Survival (IPFS)

IPFS is defined as the time from first dosing date until documented disease progression or death from any cause whichever first based on ICR as well as investigator assessment using RECIST 1.1 or appendix F in brain metastatic patients. Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment.

IPFS will be summarized based on the brain metastatic full analysis population.

IPFS will be presented in the Kaplan-Meier plot. The number of events, median (calculated from the Kaplan-Meier plot), and proportion of patients without an event at 6, 12, and 18 months will be summarized.

Overall Survival (OS)

OS will be assessed based on the date of first dose and vital status at the time of data cut off date.

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 OS will be the safety analysis population. OS will be summarized for the selected extension dose in expansion phase and extension phase. OS will be displayed using Kaplan Meier plots. The number of events, median (calculated from the Kaplan Meier plot), and proportion of patients without an event at 6, 12 and 18 months will be summarized. As appropriate, summaries of the number and percentage of patients who have died, are still in survival follow-up, are lost to follow-up and have withdrawn consent will be presented.

8.7.3. Safety Analyses

All patients who receive at least one dose of YH25448 will be included in the assessment of the safety profile (safety analysis population). At the end of the study, appropriate summaries of all safety data will be produced, as defined below.

The safety parameters are AEs, clinical laboratory parameters, vital signs, and physical examination and ECG parameters. For each safety parameter, the last non-missing safety assessment made before the date of the first administration of IP will be used as the baseline for all analyses of that safety parameter. Continuous variables will be summarized by number

of patients, mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by frequency distribution (number and percentage of patients).

8.7.3.1. Adverse Events

Data from all cycles of initial treatment will be combined in the presentation of safety data. AEs will be listed individually by patient and dose group. For patients who have a dose modification, all AEs (due to drug or otherwise) will be assigned to the initial dose group.

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.

Any AE occurring within the defined 28 day follow-up period after discontinuation of investigational product will be included in the AE summaries. 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.

All adverse events will be coded using latest version Medical Dictionary for Regulatory Activities (MedDRA). The Common Terminology Criteria for Adverse Events (CTCAE) grade will be assigned by the investigator. Severity of all AEs will be graded according to the CTCAE, Version 4.0.

The number and percentage of patients reporting AEs in each dose group will be tabulated by system organ class and preferred term; by system organ class, preferred term and severity; and by system organ class, preferred term and relationship to the IP. If more than one AE is coded to the same preferred term for the same patient, the patient will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to the IP.

The distribution of AEs by severity and relationship to the IP will be summarized by dose group.

Listings will be presented for patients with SAEs and patients with AEs leading to discontinuation, and patients who die (if any).

8.7.3.2. Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values (in SI units) and changes from the baseline values at each assessment time point will be presented by dose group for each clinical laboratory parameter.

For all laboratory variables, which are included in the current version of CTCAE, the CTCAE grade will be calculated. Summary statistics of mean, median, standard deviation, minimum, maximum and number of observations will be used.

Any qualitative assessments will be summarized for all patients using the number of patients with results of negative, trace or positive.

The number and percentage of patients with clinical significance will be tabulated by dose group. A supportive listing of patients with clinical significant changes in post-baseline values will be provided, including the patient number, study center and baseline and post-baseline values. A listing of all AEs related to clinical significant changes in laboratory values will also be provided.

8.7.3.3. Vital Signs

Descriptive statistics for vital signs (pulse rate, systolic and diastolic blood pressure, height, body weight and body temperature) and changes from baseline values (except for height) at each visit and at the end of the observational period will be presented by dose group.

8.7.3.4. 12-lead Electrocardiogram

The number and percentage of patients with clinically significant changes in post-baseline 12-lead ECG findings will be tabulated by dose group.

A supportive listing of patients with clinically significant changes in post-baseline 12-lead ECG findings will be provided, including the patient number, study center and baseline and post-baseline findings. A listing of all AEs occurring in patients who have clinically significant changes in post baseline findings will also be provided.

8.7.3.5. Physical Examination

The number and percentage of patients with clinically significant changes in post-baseline physical examination findings will be tabulated by dose group. A supportive listing of patients with clinically significant changes in post-baseline physical examination findings will be provided, including the patient number, study center and baseline and post-baseline findings. A listing of physical examination findings at screening will be provided as part of the medical history listing. Any new abnormal physical examination findings at each visit or early termination or change (worsening) since the previous physical examination will be provided in the AE listing.

8.7.4. Pharmacokinetic Analyses

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, arithmetic coefficient of variation, median, minimum, maximum, geometric mean, and geometric coefficient of variation. Parameters following single and multiple dosing will be summarized separately.

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.

Comparison of PK profiles and parameters for patients outside Korea and Korean patients after administration of single dose and multiple dose of 240 and 320 mg will be conducted. Log-transformed primary parameters, C_{max}, and AUC_{last}, $C_{max,ss}$ and AUC_{ss}, will be analyzed by analysis of variance, and point estimates and 90% confidence intervals of the geometric mean ratio (patients outside Korea /Korean patients) will be calculated.

8.7.5. Exploratory Analyses

The following variables will be summarized descriptively and may be further analyzed if deemed appropriate and details of the statistical method will be specified in accordance with the statistical analysis plan.

- Patient Reports Outcomes

Results from the exploratory analyses may be reported separately from the Clinical Study Report for the main study

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

8.8. Other Analyses

8.8.1. Subgroup Analyses

Subgroup analyses may be performed as appropriate based on the selected demographic and other baseline characteristics for the primary endpoint as well as for the other endpoints as appropriate. These will be further detailed in the SAP.

8.8.2. Analyses to Characterize the Exposure-Response Relationship

A population PK/PD approach will be used to investigate the relationship PK and selected efficacy, PD and/or safety endpoints, where deemed appropriate. The results of any such analyses may be reported separately from the Clinical Study Report for the main study.

8.9. Interim Analyses

Not applicable

8.10. Sensitivity Analyses

The same methods of analysis will be applied to analyze ORR, DoR, DCR, tumor shrinkage and PFS based on the RECIST 1.1 data assessed by the investigator. In Part C, the same methods of analysis will be applied to analyze YH25448 anticancer effects (ORR, DoR, DCR and tumor shrinkage) for all patients with a positive EGFR mutation status in the central and/or local testing.

9. ADMINISTRATIVE SECTION

9.1. Compliance

9.1.1. Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, or be prepared by the Sponsor. The investigator should not implement any deviation or changes to the protocol without prior review and documented approval from the IRB of an amendment, except where necessary to eliminate an immediate hazard(s) to study patients. Any significant deviation must be documented.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB approval, as soon as possible the deviation or change is to be submitted as soon as possible to:

- Relevant IRB(s) for review and approval
- Yuhan Corporation (Parts A, B and C)
- Janssen Research & Development, LLC (Part D)
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s) must be sent to the Sponsor.

If an amendment substantially alters the study design or increases potential risk to a patient: (1) the consent form must be revised and submitted to the IRB(s) for review and approval; (2) the revised form must be used to obtain consent from patients currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new patients prior to enrollment.

9.1.2. Monitoring

Representatives of the Sponsor must be allowed to visit all study center locations periodically to assess the data quality and study integrity. On center they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by Sponsor auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. Sponsor audit reports will be kept confidential.

The investigator must notify the Sponsor promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to the Sponsor.

9.1.3. Investigational Site Training

Sponsor will provide appropriate investigational staff training prior to study initiation. Training topics will include but are not limited to: ICH-GCP, AE reporting, study details and procedure, study documentation, informed consent, and enrollment method.

For centers using the Sponsor electronic data capture tool, each individual making entries and/or corrections on electronic CRFs must meet Sponsor training requirements and must only access the Sponsor electronic data capture tool using the unique user account provided by the Sponsor. User accounts are not to be shared or reassigned to other individuals.

For electronic CRFs, corrections are made through the Sponsor electronic data capture tool that generates an automated audit trail including date and timestamp, full name of the person making the correction and original entry. The system also prompts the user to document the reason for the change which is also recorded in the audit trail.

Each individual electronically signing electronic CRFs must meet Sponsor training requirements and must only access the Sponsor electronic data capture tool using the unique user account provided by the Sponsor. User accounts are not to be shared or reassigned to other individuals.

9.2. Records Retention

The investigator must retain investigational product disposition records, copies of CRFs (or electronic files), and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the Sponsor, whichever is longer. The investigator must contact the Sponsor prior to destroying any records associated with the study. The Sponsor will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer is to be given in writing to the Sponsor.

9.2.1. Case Report Forms

Each investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation for each individual treated in the investigation. Data reported on the CRFs that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

For centers using the Sponsor's electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the Pregnancy Surveillance Form. Patients are to be identified by birth date and patient number, where applicable. All requested information must be entered on the CRF in the spaces provided. If the entry for an item is not available or is not applicable, it must be documented as such (N/A); do not leave any space blank. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by the Sponsor. Electronic data transfer is acceptable.

The confidentiality of records that may be used to identify patients must be protected, respecting privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document the signatures and initials of all persons authorized to make entries and/or corrections on the CRFs. The completed CRF, including any paper SAE report or Pregnancy Surveillance Forms, must be promptly reviewed, signed, and dated by an investigator or sub-investigator, who is a qualified physician. For electronic CRFs, the review and approval/signature are completed electronically through the Sponsor electronic data capture tool. The investigator must retain a copy of the CRFs, including records of the changes and corrections.

9.2.2. Investigational Product Records

It is the responsibility of the principal investigator to ensure that a current record of investigational product disposition is maintained at each study center where investigational product is inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

- quantity received and placed in storage area
- quantity currently in storage area
- label ID number or batch number and use by date or re-test date
- dates and initials of person responsible for each investigational product inventory entry/movement
- quantity dispensed to and returned by each patient, including unique patient identifiers
- quantity transferred to another areas/centers for dispensing or storage
- any details of non-study use (eg, lost, wasted, broken)
- quantity returned to the Sponsor

The Sponsor will provide forms to facilitate inventory control if the staff at the investigational center does not have an established system that meets these requirements.

9.3. Return and Destruction of Investigational Product

9.3.1. Return of Investigational Product

Upon completion or termination of the study, all unused and/or partially used investigational product must be returned to the Sponsor.

It can be destroyed locally as permitted by local or site regulations, if needed. (Part D)

All investigational product returned to the Sponsor must be accompanied by the appropriate documentation and clearly identified by protocol number on the outermost shipping container. Returned supplies including empty vials should be in the original containers (eg, vials that have clinical labels attached). The return of unused investigational product(s) should be arranged by the responsible Study Monitor.

9.3.2. Destruction of Investigational Product

At study close-out, the Sponsor will destroy all used and unused study drug as per SOP and relative regulatory. Investigational sites will return to the Sponsor all used and unused study drug, packaging and drug labels appropriately. A copy of completed drug accountability will be provided to the Sponsor.

9.4. Publications

The data collected during this study are confidential and proprietary to the Sponsor. Any publications or abstracts arising from this study require prior written approval from and must adhere to the Sponsor's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to the Sponsor at the earliest practicable time for review, but in any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. The Sponsor retains the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for purposes of filing a patent application.

10. GLOSSARY OF TERMS

Term	Definition
Adverse Event	Any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient for clinical investigation patient administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including abnormal laboratory findings, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.
Adverse Drug Reaction	In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.
Expedited Safety Report (ESR)	Important findings which may be reported by the Sponsor: SUSAR, increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study patients, clinically significant safety findings from a nonclinical (e.g., animal) study, important safety recommendations from a study data monitoring committee, or Sponsor decision to end or temporarily halt a clinical study for safety reason
SUSAR	Suspected (certainly, probably, or possibly related to the investigational product), Unexpected Serious Adverse Reactions
Unexpected Adverse Drug Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product)

LIST OF ABBREVIATIONS

Term	Definition
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
$AUC_{0\ 24}$	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
BAD	Biologically Active Dose
BBB	Blood Brain Barrier
BrM	Brain Metastasis
C_{CSF}	CSF concentration
C_{DX}	Trough concentration on Day X
cfDNA	Circulating tumor deoxyribonucleic acid
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
CNS	Central Nervous System
CR	Complete response
CRF	Case report form (electronic/paper)
CSF	Cerebrospinal fluid
CT	Computerised tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Co-operative Oncology group
EGFR	Epidermal growth factor receptor

EGFR m+	Epidermal growth factor receptor single activating mutation positive
EORTC	European Organisation for Research and Treatment of Cancer
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HED	Human equivalent dose
HNSTD	Highest non-seriously toxic dose
HRQoL	Health Related Qulaity of Life
IATA	International Air Transport Association
IB	Investigators brochure
IP	Investigational Product
ICH	International Committee on Harmonisation
MAD	Maximum Absorbable Dose
MFDS	Ministry of Food and Drug Safety
MR	Metabolic ratio
MR_{ss}	Metabolic ratio at steady state
MRI	Magnetic resonance imaging
MRSD	Maximum Recommended Starting Dose
MTD	Maximum tolerated dose
NE	Not evaluable
NOEL	No observed effect level
NSCLC	Non Small Cell Lung Cancer
NTL	Non-target lesion
ORR	Objective Response Rate
OS	Overall Survival
PD	Progression of disease
pEGFR	phosphorylated EGFR
PFS	Progression free survival
PK	Pharmacokinetics
PR	Partial response
PRO	Patient Reported Outcomes
QCP	Quantitative Clinical Pharmacology

QD	Once Dialy
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
Rac	Accumulation ratio
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SD	Stable disease
SRC	Safety review committee
STD10	Severely toxic dose in 10% of rodents
$t_{1/2}$	Apparent terminal elimination half-life
TKI	Tyrosine kinase inhibitor
T_{max}	Time to reach C_{max}
$T_{max,ss}$	Time to reach $C_{max,ss}$
ULN	Upper limit of normal
Vd/F	Apparent volume of distribution
λ_z	Apparent terminal elimination rate constant

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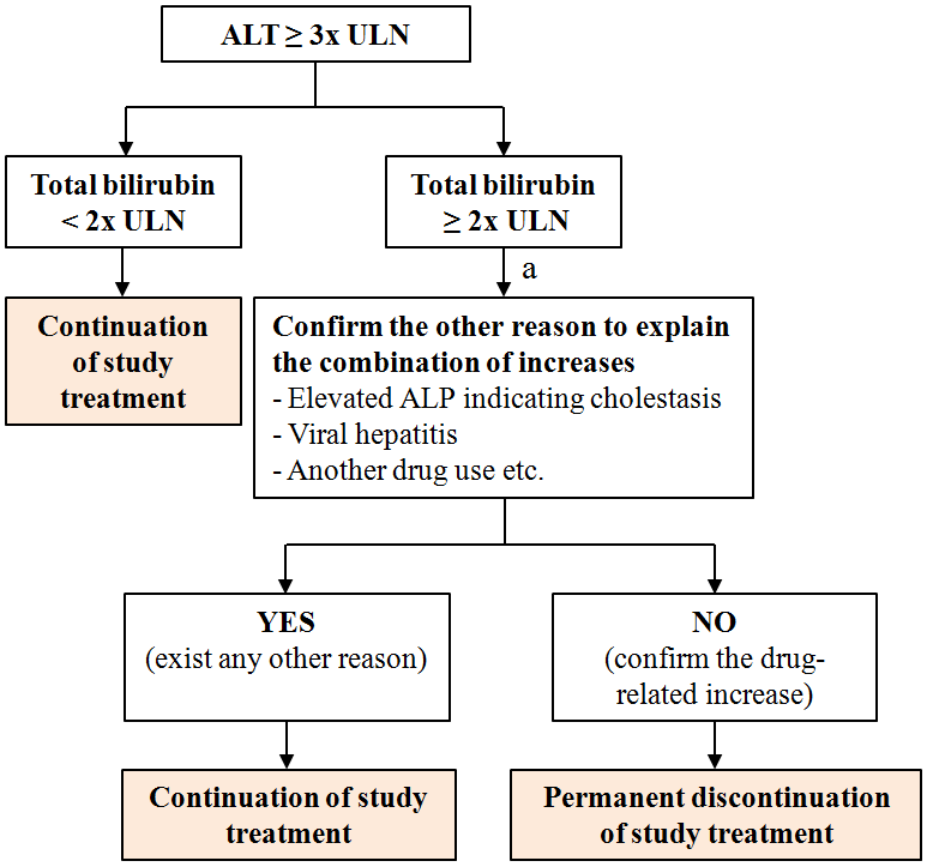
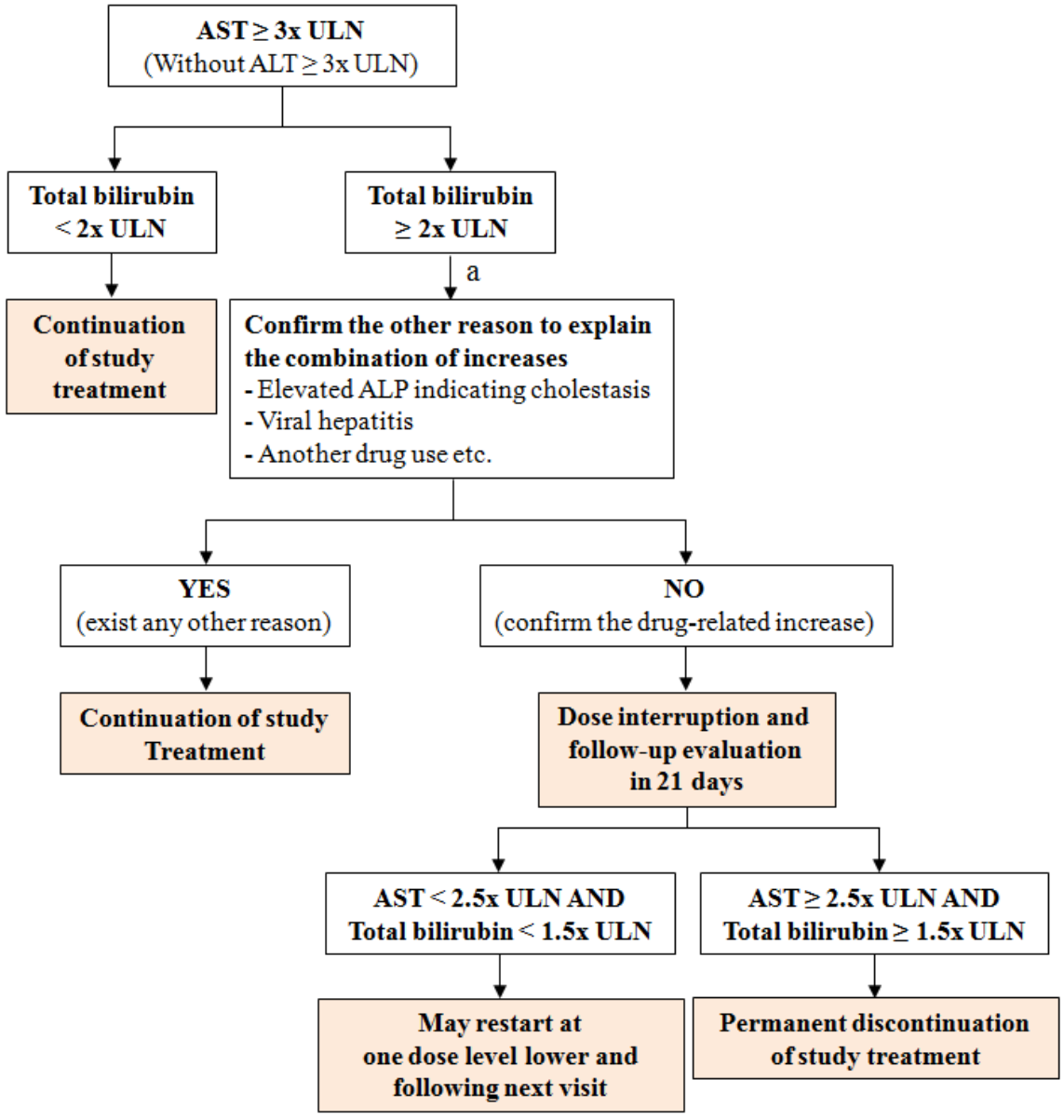
Appendix A. Algorithm for Continuation, Dose Modification or Discontinuation of YH25448 Based on Increases of Liver Biochemistry (Hy's Law[17])

A. Increases in ALT and Total bilirubin



B. Increases in AST and Total bilirubin



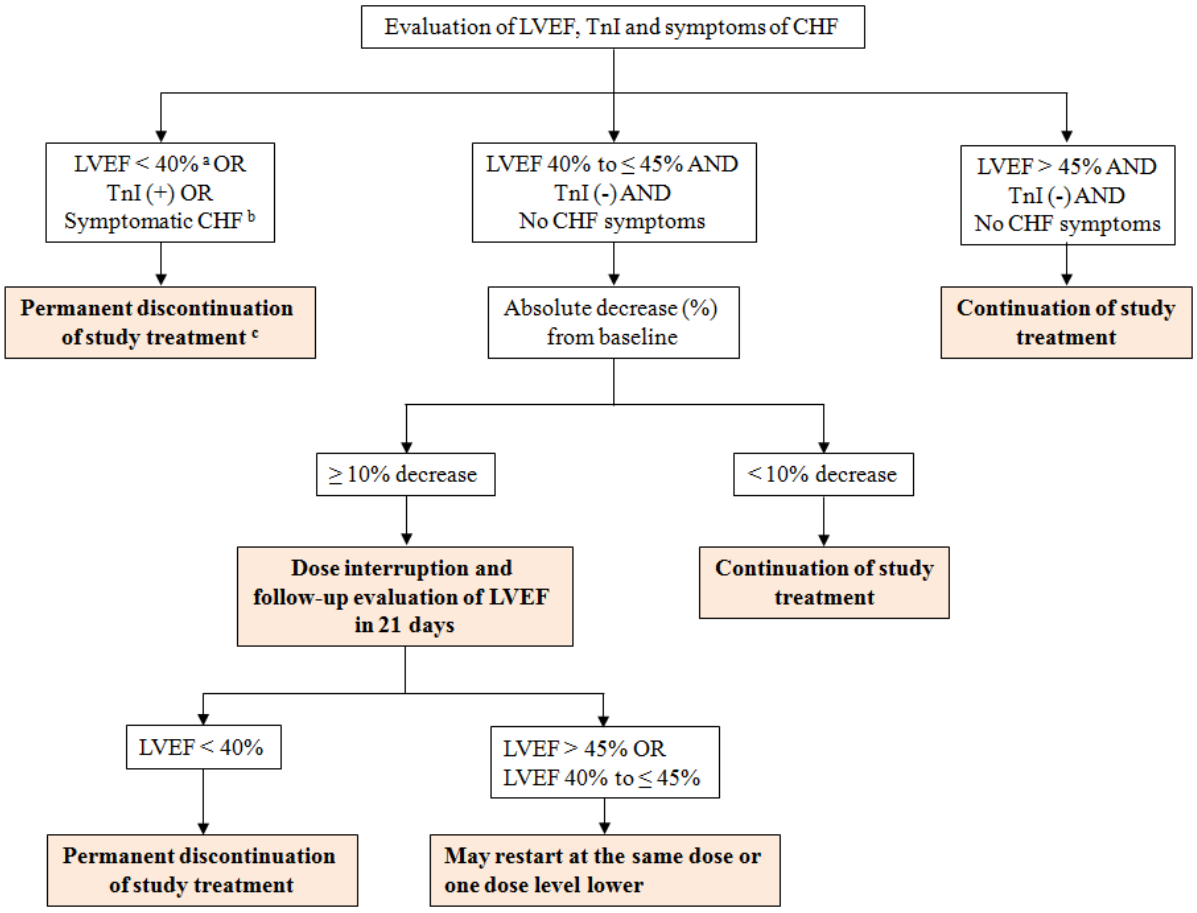
AST = Aspartate Aminotransferase; ALT = Alanine Aminotransferase; ULN = Upper Limit of Normal;
ALP = Alkaline Phosphatase
[a] The Investigator must complete the specific CRF form and inform the Monitoring Team within 24 hours

References

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Appendix B. Algorithm for Continuation and Discontinuation of YH25448 Based on LVEF and TnI Assessments in Patients



CHF congestive heart failure; LVEF left ventricular ejection fraction; TnI Troponin I

[a] LVEF < 40% can be repeated within 21 days, and YH25448 should be discontinued if LVEF < 40% is confirmed. YH25448 should be held while the repeat LVEF is obtained.

[b] Class ≥ 3 as defined by New York Heart Association (NYHA) classification (2014)

Class I	No limitations. Ordinary physical activity does not cause undue fatigue, dyspnoea or palpitations (asymptomatic LV dysfunction).
Class II	Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnoea or angina pectoris (mild CHF)
Class III	Marked limitation of physical activity. Less than ordinary physical activity leads to symptoms (moderate CHF).
Class IV	Unable to carry on any physical activity without discomfort. Symptoms of CHF present at rest (severe CHF)

[c] **Parts A, B, and C**

If TnI is determined to be positive (TnI+), it will be re-tested by central laboratory within 3 days before permanent discontinuation of study treatment. A positive result from the TnI test means when the laboratory value exceeds the ULN as per each site or central laboratory range.

Part D

TnI is positive (TnI+) when the laboratory value exceeds the ULN as per local laboratory range and is clinically significant for a cardiac event. If TnI laboratory value exceeds the ULN, it will be re-tested by local laboratory within 3 days. If considered clinically significant, study treatment will be permanently discontinued after consultation with the Sponsor medical monitor. In Part D, central laboratory confirmation of TnI local laboratory value is not required.

Appendix C. International Airline Transportation Association (IATA) Guidance Document

Labeling and Shipment of Biohazard Samples

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg. Ebola, Lassa fever virus

- are to be packed and shipped in accordance with IATA Instruction 602

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg. Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations.
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging.
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content.
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable.
- Samples routinely transported by road or rail are patient to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix D. Ethical and regulatory requirements

Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP) guidelines, applicable regulatory requirements and the Sponsor policy on Bioethics and Human Biological Samples.

Ethics and regulatory review

An Ethics Committee should approve the final Clinical Study Protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients. This will include approval of the exploratory biomarker and pharmacogenetic research and associated consent(s) forms. The investigator/The Head of the study center will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff. In Japan, the head of the study center will ensure the distribution of these documents to the applicable IRB, and the Principal Investigator to the Investigator and study site staff.

The opinion of the Ethics Committee should be given in writing. The investigator should submit the written approval to the Sponsor before enrolment of any patient into the study. If applicable this approval should clearly state that the exploratory biomarker and pharmacogenetic research is approved.

The Ethics Committee should approve all advertising used to recruit patients for the study.

The Sponsor should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the Ethics Committee annually.

The Sponsor will handle the distribution of any of these documents to the national regulatory authorities.

TheSponsor will provide Regulatory Authorities, Ethics Committees and Principal Investigators (in Japan, also the Head of the study center) with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

Each Principal Investigator is responsible for providing the Ethics Committees/Institutional Review Board (IRB) with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product.

Informed consent

Any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation should be described in the informed consent form that is approved by an Ethics Committee.

The Principal Investigator at each centre will:

- Ensure that each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study and the optional exploratory biomarker and genetic research component(s)
- Ensure that each patient is notified that they are free to withdraw from the study or the research components at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure each original, signed Informed Consent Form is stored in the Investigator's Study File/medical records
- Ensure a copy of each signed Informed Consent Form is given to the patient

The exploratory biomarker and genetic research component(s) of this study are voluntary and the patient may participate in the main study without participating in the exploratory biomarker and/or genetic research part(s) of the study. To participate in the exploratory biomarker and/or genetic component of the study the patient should sign and date the consent form for the main study and as applicable separate consent forms for the exploratory biomarker and/or the genetic components of the study.

Changes to the protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and the Sponsor.

If there are any substantial changes to the Clinical Study Protocol, then these changes will be documented in a Clinical Study Protocol Amendment and where required in a new version of the protocol (Revised Protocol).

The amendment should be approved by each Ethics Committee and if applicable, also the national regulatory authority, before implementation. Local requirements should be followed for Revised Protocols.

The Sponsor will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator.

If a protocol amendment requires a change to a centre's Informed Consent Form, the Sponsor and the centre's Ethics Committee should approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

Audits and inspections

Authorized representatives of the Sponsor, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator will contact the Sponsor immediately if contacted by a regulatory agency about an inspection at the centre.

Appendix E. Data and study management

Patient data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

Due to the exploratory nature of the biomarker and genetic research, there will be no routine communication of these results to patients. The Sponsor will not provide individual results to patients, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an Sponsor Study Physician or an investigator might know a patient's identity and also have access to his or her genetic data. Also regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

Pre-study activities

Before the first patient is entered into the study, it is necessary for a representative of the Sponsor to visit the investigational study center to:

- Determine the adequacy of the facilities
- Determine availability of appropriate patients for the study
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the investigator

Training of study site personnel

Before the first patient is entered into the study, a Sponsor representative will visit the study center to review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also to train them in any study specific procedures including collection of samples and the WBDC system utilised. The additional requirements for the collection of the patients' samples for the exploratory biomarker and genetic research will also be clarified.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of the staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all staff members involved in the study (medical, nursing and other staff).

Source data
Refer to the Clinical Study Agreement for location of source data.

Monitoring of the study
During the study, a Sponsor representative will have regular contacts with the study centers, including visits to:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol including the specific requirements of the biomarker and genetic research, that data are being accurately and timely recorded in the CRFs, and that investigational product accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of the Informed Consent Form(s)of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)
- If applicable, ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient

The Sponsor representative will be available between visits if the investigator(s) or other staff at the centre needs information and advice about the study conduct.

Data management by Sponsor/**delegate**
Data management will be performed by the Cognizant Data Management Centre.

Data entered in the WBDC system or data captured electronically will be immediately saved to the applicable database and changes tracked to provide an audit trail.

The data collected through third party sources will be obtained and reconciled against study data.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the Sponsor Drug Dictionary. All coding will be performed by the Medical Coding Team at the Sponsor Data Management Centre/other party.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment-revealing data may thereafter be added and the final database will be locked.

Genotype data generated in this study will be stored in the Sponsor applicable database, or other appropriate secure system, separate from the database used for the main study.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database. The results from this genetic research will be reported separately from the Clinical Study Report for the main study.

Study agreements
The Principal Investigator at each centre should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, the terms of the Clinical study Agreement shall prevail.

Specific reference to requirements relating to this optional biomarker and genetic research will be included in the study agreement(s).

Agreements between the Sponsor and the Principal Investigator should be in place before any study-related procedures can take place, or patients be enrolled.

Archiving of study documents
The investigator follows the principles outlined in the Clinical Study Agreement.

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

The study may be terminated at individual centres if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow. The Sponsor may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with YH25448.

Appendix F. Guidelines for Evaluation of Objective Tumor Response Using RECIST 1.1 (Response Evaluation Criteria in Solid Tumors) FOR ASSESSMENT OF INTRACRANIAL AND EXTRACRANIAL DISEASE[18]

Introduction

This appendix details the implementation of RECIST 1.1 Guidelines with regards to Investigator assessment of tumor burden including protocol-specific requirements for this study. The criteria has been modified to allow the separate assessment of CNS and extracranial disease in patients with measurable brain metastases.

Definition of measurable, non-measurable, target and non-target lesions

Patients will be entered to different phases on this study according to the following inclusion criteria

Patients without measurable BrM (except patients with measurable brain metastases), at least one measurable extracranial lesion not previously irradiated or biopsied within the screening period, (passed over 14 days at least in case of biopsied) that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements.

BrM patients: (patients with measurable brain metastases), at least one measurable intracranial lesion has progressed or not responded to prior radiotherapy that can be accurately measured at baseline as ≥ 10 mm in the longest diameter by magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements.

Progression will be assessed as the visit response if there is progression extracranial disease and/or intracranial disease. An overall visit response will be derived by combining the intracranial and extracranial disease time point responses.

Measurable:

Extracranial Lesion: An extracranial lesions not previously irradiated or biopsied within the screening period, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements. Patients with measurable brain metastases are not required to have measurable extracranial disease

Brain metastasis: An intracranial brain lesion has progressed or not responded to prior radiotherapy that can be accurately measured at baseline as ≥ 10 mm in the longest diameter by

magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements. Patients with measurable brain metastases are not required to have measurable extracranial disease.

Non-measurable:

- All other extracranial lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15mm short axis at baseline*).
- All other intracranial lesions, including small lesions (longest diameter < 10 mm)
- Truly non-measurable lesions include the following: bone lesions, ascites, pleural / pericardial effusion, and inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses /abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.
- Previously irradiated extracranial lesions**
- Previously irradiated intracranial lesions which have not progressed or responded to prior radiotherapy**
- Skin lesions assessed by clinical examination

* Nodes with <10mm short axis are considered non-pathological and should not be recorded or followed as NTL.

**Localized post-radiation changes which affect lesion sizes may occur

Special Cases:

- Lytic bone lesions or mixed lytic blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.
- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient. These should be selected as target lesions.

Target lesions:
Extracranial lesions: A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as target lesions (TL) at baseline. Intracranial disease will be assessed separately.

Intracranial lesions: A maximum of 5 measurable lesions.

Non-Target lesions:
All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline.

Extracranial and intracranial disease (brain metastases) will be assessed separately.

Methods of ASSESSMENT
The same method of assessment and the same technique should be used to characterize each identified and recorded lesion at baseline and during follow-up visits.

A summary of the methods to be used for RECIST 1.1 assessment is provided below and those excluded from tumor assessments for this study are highlighted, with the rationale provided.

Table 1. Extracranial disease: Summary of Methods of Assessment

Target Lesions	Non-Target Lesions	New Lesions
CT (preferred)	CT (preferred)	CT (preferred)
MRI	MRI	MRI
	Clinical examination	Clinical examination
	X-ray, Chest x-ray	X-ray, Chest x-ray
		Ultrasound
		Bone Scan
		FDG-PET

Table 2. Intracranial disease: Summary of Methods of Assessment

Target Lesions	Non-Target Lesions	New Lesions
MRI	MRI	MRI

CT and MRI (extracranial and intracranial disease)
CT and MRI are generally considered to be the best currently available and reproducible methods to measure TL selected for response assessment and to assess NTL and identification of any new lesions for extracranial disease

In this study it is recommended that CT examinations of the chest and abdomen (including liver and adrenal glands). CT examination with intravenous (i.v.) contrast media administration is the preferred method.

MRI is generally considered to be the best currently available and reproducible method for assessment of intracranial disease and for this study to measure TL selected for response assessment and to assess NTL and identification of any new lesions.

Clinical examination (extracranial disease only)
Clinical examination will not be used for assessment of TL. Clinically detected lesions can be selected as target lesions if they are assessed by CT or MRI scans. Clinical examination can be used to assess NTL and to identify the presence of new lesions.

X-ray (extracranial disease only)
Chest X-ray

Chest x-ray assessment will not be used for assessment of TLs as they will be assessed by CT examination or MRI examination. Chest X-ray can, however, be used to assess NTL and to identify the presence of new lesions.

Plain X-ray

Plain x-ray may be used as a method of assessment for bone NTL and to identify the presence of new bone lesions.

Ultrasound (extracranial disease only)
Ultrasound examination will not be used for assessment of TL and NTLs as it is not a reproducible method, does not provide an accurate assessment of tumor size and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed then new lesions should be confirmed by CT or MRI examination.

Endoscopy and laparoscopy (extracranial and intracranial disease)
Endoscopy and laparoscopy will not be used for tumor assessments as they are not validated in the context of tumor assessment.

Tumor markers (extracranial and intracranial disease)
Tumor markers will not be used for tumor response assessments as per RECIST 1.1.

Cytology and histology (extracranial and intracranial disease)
Histology will not be used as part of the tumor response assessment as per RECIST 1.1.

CSF cytology assessments will be performed and reported separately for the assessment of clinical response for patients with leptomeningeal disease.

Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is required when the measurable tumor has met criteria for response or stable disease. In such circumstances, the cytology is necessary to differentiate between response / stable disease (an effusion may be a side effect of the treatment) and progressive disease (if the

neoplastic origin of the fluid is confirmed). Where cytology findings are not available, any effusion that significantly worsens (from trace to large) or appearance of clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be progression of NTL, or disease progression due to new lesions.

Isotopic bone scan (extracranial disease only)
Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI or X-ray at baseline should be recorded as NTL and followed by the same method as per baseline assessment.

Isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The Investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI and x-ray is recommended where bone scan findings are equivocal.

FDG-PET scan (extracranial disease only)
FDG-PET scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will be recorded where there is positive FDG uptake* not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

* A positive FDG-PET scan lesion should be reported only when an uptake greater than twice that of the surrounding tissue is observed.

Tumor response evaluation
Schedule of evaluation
Imaging assessments will be performed using CT scan of the chest and abdomen (including liver and adrenal glands) at base-line within 28 days of treatments start and then every 6 weeks ± 1week until objective disease progression or withdrawal from study. In addition all patients will have a brain MRI scan at baseline and at follow-up in patients with confirmed brain metastases on the baseline brain scan. In addition additional areas should be investigated based on the signs and symptoms of the patient. Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits.

Target lesions (TL)

Documentation of target lesions (extracranial lesions)

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), representative of all lesions involved should be identified as TL at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes) on the extracranial lesions RECIST eCRF. All measurements should be recorded in millimeters. At baseline the sum of the diameters for all TL will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TL will be calculated and reported as the follow-up sum of diameters.

Documentation of target lesions (intracranial lesions)

A maximum of 5 measurable lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes) on the intracranial lesions RECIST eCRF. All measurements should be recorded in millimeters. At baseline the sum of the diameters for all TL will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TL will be calculated and reported as the follow-up sum of diameters.

Special cases:

- For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.
- If the CT/MRI slice thickness used is > 5mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.
- If a TL splits into two or more parts, then record the sum of the diameters of those parts.
- If two or more TLs merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).

- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned for extracranial and intracranial lesion, respectively. If an accurate measure can be given, this should be recorded, even if it is below 5mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.
- When a TL has had any intervention e.g. radiotherapy, embolization, surgery etc., during the study, the size of the TL should still be provided where possible.

Evaluation of target lesions (extracranial and intracranial lesions)
This section provides the definitions of the criteria used to determine objective tumor visit response for TL.

Table 3. Evaluation of target lesions

Complete Response (CR)	Disappearance of all target lesions since baseline. Any pathological lymph nodes selected as target lesions must have a reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm for extracranial and intracranial lesion, respectively.
Not Evaluable (NE)	Only relevant if any of the target lesions were not assessed or not evaluable or had a lesion intervention at this visit. Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a target lesion response

Non-Target lesions (NTL)
Evaluation of non-target lesions (extracranial lesions)
All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit an overall assessment of the NTL response should be recorded by the Investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit.

Evaluation of non-target lesions (intracranial lesions)
All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit an overall assessment of the NTL response should be recorded by the Investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit.

In addition the investigator will be asked to record an assessment for leptomeningeal disease of complete response, responding, stable or progressing in addition to assessment as part of the non-target lesions for intracranial response assessment.

Table 4. Evaluation of Non-Target Lesions (extracranial and intracranial lesions)

Complete Response (CR)	Disappearance of all non-target lesions since baseline. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non CR/Non PD	Persistence of one or more NTL
Progression (PD)	Unequivocal progression of existing non-target lesions. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Not Evaluable (NE)	Only relevant when one or some of the non-target lesions were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall non-target lesion assessment at this visit. Note: For patients without target lesions at baseline, this is relevant if any of the non-target lesions were not assessed at this visit and the progression criteria have not been met.

To achieve ‘unequivocal progression’ on the basis of non-target lesions, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest ‘increase’ in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

New Lesions (extracranial and intracranial disease)
Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor.

If a new lesion is equivocal, for example because of its small size, the treatment and tumor assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

Symptomatic deterioration

Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

Patients with 'symptomatic deterioration' requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumor assessments where possible until objective disease progression is observed.

Evaluation of Visit Response

The visit response will be derived separately for extracranial and intracranial disease separately using the algorithm shown in table 5.

Table 5. 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

CR complete response, PR partial response, SD stable disease, PD progressive disease,

NE not evaluable, NA not applicable (only relevant if there were no TL/NTLs at baseline).

Overall visit response

The overall visit response will be using the algorithm shown in table 6 which is analogous to the RECIST 1.1 approach where brain lesions are assessed as non-target lesions.

Table 6. 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
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

CR complete response, PR partial response, SD stable disease, PD progressive disease, NE not evaluable, NA not applicable

Confirmation of response

Imaging for confirmation of response (CR or PR) for intracranial or extra cranial disease should be performed at the next scheduled visit (certainly no less than 4 weeks) following the date the criteria for response were first met.

Central Review

The Contract Research Organization (CRO) appointed by Yuhan to perform the independent central review for this study will provide specification for radiological imaging protocols in standard acquisition guidelines documentation.

Appendix G. GUIDANCE REGARDING POTENTIAL INTERACTIONS WITH CONCOMITANT MEDICATIONS

The use of any natural/herbal products or other "folk remedies" (e.g. Ginseng and other Traditional Chinese Medicine) should be discouraged, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the eCRF.

YH25448 is an investigational drug for which no data on in vivo interactions are currently available. Based on in vitro data and predicted clinical exposure data, YH25448 is considered unlikely to cause clinically significant drug interactions through inhibition or induction of cytochrome P450 enzyme activity.

In vitro data have shown that the principal CYP enzymes responsible for the Phase I metabolism of YH25448 is CYP3A4/5. Therefore, drugs inhibiting CYP3A4/5 metabolism are recommended not to combine with YH25448. Drugs inducing CYP3A4/5 metabolism should also be avoided to combine with YH25448 if possible.

YH25448 is an inhibitor of P-gp, MRP4, and BCRP, which increases the bioavailability of concomitant medication affecting p-gp, MRP4, and BCRP substrates by restricting intestinal P-gp and BCRP. Therefore, the plasma concentration of digoxin and P-gp substrates should be monitored closely and their dosage can be adjusted properly.

It is recommended that the starting and maintenance dose of statins should be as low as possible and should be guided by the statin label. Monitoring of low- density lipoprotein (LDL) cholesterol levels is advised. If the patient experiences any potentially relevant adverse events suggestive of muscle toxicity including unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever, the statin should be stopped, creatine kinase (CK) levels should be checked, and any appropriate further management should be taken.

Patients taking warfarin should be monitored regularly for changes in prothrombin time or INR.

Drugs inhibiting CYP3A4/5 metabolism that The Sponsor recommend are not combined with YH25448

The contribution of Phase I metabolism to the total clearance of YH25448 is currently unknown but, to ensure patient safety, the following inhibitors of CYP3A4/5 must not be used during this study for any patient receiving YH25448 and the inhibitors are not only limited to the table below.

Table 1. Drug inhibiting CYP3A4/5

Contraindicated drugs	Withdrawal period prior to YH25448 start
ketoconazole, itraconazole, indinavir, saquinovir, nelfinavir, atazanavir, amprenavir, fosamprenavir, troleandomycin, telithromycin, fluconazole, nefazodone, cimetidine, aprepitant, miconazole, fluvoxamine	1 week
amiodarone	27 weeks
erythromycin, clarithromycin, verapamil, ritonavir, diltiazem	2 weeks

This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to strongly modulate CYP3A4/5 activity. Appropriate medical judgment is required. Please contact the Sponsor with any queries you have on this issue.

Drugs inducing CYP3A4 metabolism that the **Sponsor recommend are not combined with YH25448**

To avoid potential reductions in exposure due to drug interactions, the following CYP3A4/5 inducers should be avoided if possible.

Table 2. Drug inducing CYP3A4/5

Contraindicated drugs	Withdrawal period prior to YH25448 start
phenytoin, rifampicin, St. John's Wort, carbamazepine, primidone, griseofulvin, barbiturates, troglitazone, pioglitazone, oxcarbazepine, nevirapine, efavirenz, rifabutin	3 weeks
Phenobarbitone	5 weeks

This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to strongly modulate CYP3A4/5 activity. Appropriate medical judgment is required. Please contact the Sponsor with any queries you have on this issue.

Anti-convulsive drugs can be given to treat seizures at the discretion of the investigator when necessary.

Dexamethasone, a commonly used steroid to relieve brain edema, is a weak CYP3A4/5 inducer which may increase YH25448 clearance. Steroid is allowed to use in this study but must be recorded in the eCRF.

Drugs that may prolong QT interval
The drugs listed in this section are taken from information provided by The Arizona Center for Education and Research on Therapeutics and The Critical Path Institute, Tucson, Arizona and Rockville, Maryland. Ref: http://www.arizonacert.org/medical-pros/drug-lists/drug-lists.htm.

Drugs known to prolong QT interval
The following drugs are known to prolong QT interval or induce Torsades de Pointes and should not be combined with YH25448. Recommended withdrawal periods following cessation of treatment with these agents are provided in the table.

Table 3. Drugs prolonging QT interval

Contraindicated drug	Withdrawal period prior to YH25448 start
Clarithromycin, droperidol, erythromycin, procainamide	2 days
Cisapride, disopyramide, dofetilide, domperidone, ibutilide, quinidine, sotalol, sparfloxacin, thioridazine	7 days
Bepridil, chlorpromazine, halofantrine, haloperidol, mesoridazine	14 days
Levomethadyl, methadone, pimozide	4 weeks
Arsenic trioxide	6 weeks*
Pentamidine	8 weeks
Amiodarone, chloroquine	1 year

* Estimated value as pharmacokinetics of arsenic trioxide has not been studied

Drugs that may possibly prolong QT interval

The use of the following drugs is permitted (notwithstanding other exclusions and restrictions) provided the patient has been stable on therapy for the periods indicated.

Table 4. Drugs that may possibly prolong QT interval

Drug	Minimum treatment period on medication prior to YH25448 start
Alfuzosin, chloral hydrate, ciprofloxacin, dolasetron, foscarnet, galantamine, gemifloxacin, isridipine, ketoconazole, levofloxacin, mexiletine, nicardipine, octreotide, ofloxacin, ondansetron, quetiapine, ranolazine, telithromycin, tizanidine, vardenafil, venlafaxine, ziprasidone	2 days
Amantadine, amitriptyline, amoxapine, clozapine, doxepin, felbamate, flecainide, fluconazole, fosphenytoin, gatifloxacin, granisetron, imipramine, indapamide, lithium, moexipril/HCTZ, moxifloxacin, risperidone, roxithromycin, sertraline, trimethoprin-sulfa, trimipramine, voriconazole	7 days
Azithromycin, citalopram, clomipramine, itraconazole, nortriptyline, paroxetine, solifenacin, tacrolimus	14 days
Fluoxetine	5 weeks
Protriptyline	6 weeks
Tamoxifen	8weeks

Appendix H. PATIENT REPORTED OUTCOMES (QLQ C-30)

EORTC QLQ-C30 (version3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
□□□□
Your birthdate (Day, Month, Year):
□□□□□□□□
Today's date (Day, Month, Year):

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4

10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4
17.	Have you had diarrhea?	1	2	3	4
18.	Were you tired?	1	2	3	4
19.	Did pain interfere with your daily activities?	1	2	3	4
20.	Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21.	Did you feel tense?	1	2	3	4
22.	Did you worry?	1	2	3	4
23.	Did you feel irritable?	1	2	3	4
24.	Did you feel depressed?	1	2	3	4
25.	Have you had difficulty remembering things?	1	2	3	4
26.	Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27.	Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28.	Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix I. PATIENT REPORTED OUTCOMES (QLQ LC-13)

EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :		Not at All	A Little	Quite a Bit	Very Much
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

Appendix J. PATIENT REPORTED OUTCOMES (QLQ BN-20)

EORTC QLQ – BN-20

Patients sometimes report that they have the following symptoms. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

Please fill in your initials:
□□□□
Your birthdate (Day, Month, Year):
□□□□□□□□
Today's date (Day, Month, Year):

During the past week:

		Not at All	A Little	Quite a Bit	Very Much
1.	Did you feel uncertain about the future?	1	2	3	4
2.	Did you feel you had setbacks in your condition?	1	2	3	4
3.	Were you concerned about disruption of family life?	1	2	3	4
4.	Did you have headaches?	1	2	3	4
5.	Did your outlook on the future worsen?	1	2	3	4
6.	Did you have double vision?	1	2	3	4
7.	Was your vision blurred?	1	2	3	4
8.	Did you have difficulty reading because of your vision?	1	2	3	4
9.	Did you have seizures?	1	2	3	4
10.	Did you have weakness on one side of your body?	1	2	3	4
11.	Did you have trouble finding the right words to express yourself?				
	1 2 3				
12.	Did you have difficulty speaking?	1	2	3	4
13.	Did you have trouble communicating your thoughts?	1	2	3	4
14.	Did you feel drowsy during the daytime?	1	2	3	4
15.	Did you have trouble with your coordination?	1	2	3	4

16.	Did hair loss bother you?	1	2	3	4
17.	Did itching of your skin bother you?	1	2	3	4
18.	Did you have weakness of both legs?	1	2	3	4
19.	Did you feel unsteady on your feet?	1	2	3	4
20.	Did you have trouble controlling your bladder?	1	2	3	4

Appendix K. Information for Sponsor and Principal Investigators
[Principal Investigators]

(Dated on 09Dec2020)

PPD

PPD

PPD

PPD

[Sponsor]

Sponsor Name	Address
Yuhan Corporation	74, Noryangjin-ro, Dongjak-gu, Seoul, 06927, Korea
Janssen Research & Development, LLC	920 U.S. Route 202, Raritan, NJ, 08869, United States of America

Signature

User	Date	Reason
PPD	19-Nov-2021 20:14:32 (GMT)	Document Approval

Janssen Research & Development *

Clinical Protocol

COVID-19 Appendix

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) Part D

Protocol 73841937NSC2001; Phase 1/2, Part D
(also known as YH25448-201, Part D)

JNJ-73841937 (YH25448)

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; Janssen Sciences Ireland UC; Janssen Biopharma Inc.; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).

Status: Approved
Date: 28 Apr 2020
Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-RIM-49311, 1.0

THIS APPENDIX APPLIES TO ALL CURRENTLY APPROVED VERSIONS OF PROTOCOL 73841937NSC2001

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

COVID-19 APPENDIX

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; and changes in hospital or clinic procedures required to address the COVID-19 challenge, including study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study related management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's safety is considered to be at risk, study intervention will be discontinued, and study follow-up will be conducted as outlined in the protocol.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up. However, if scheduled visits cannot be conducted in person at the study site it is suggested that they be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed in order to continue participant monitoring in accordance with the protocol where possible. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Modifications to protocol-required assessments may be permitted in alignment with this COVID-19 Appendix only after consultation with the participant, investigator, and the sponsor. Missed assessments, study visits required by the protocol will still be considered protocol deviations and captured as "COVID-19 related" in the clinical trial management system. Study drug interruptions or discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the case report form (CRF).

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a participant has tested positive for SARS-CoV-2 (COVID-19), the investigator should contact the Sponsor's Medical Monitor to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic will be summarized in the clinical study report.

The guidance here-in is applicable until the clinical site returns to pre-pandemic operational capacity and practices:

- Due to the COVID-19 pandemic, screening and enrollment into the 73841937NSC2001 Part D study has been temporarily stopped at all study sites
- The safety of the participants currently on study is a priority. Please continue with all scheduled visits, safety assessments, and radiographic assessments as far as possible.
- If safety assessments such as echocardiography/MUGA, ophthalmologic exam and laboratory tests cannot be performed at the active clinical study site, patients will be permitted to use other facilities (at hospitals that have certified testing facilities). All results must be shared with the clinical study site and laboratory results must be available for the investigator to review prior to dosing. Copies of the results should be included in the participant's study chart as a source document.
- In the event the participant cannot visit the active clinical study site, telemedicine is allowed for the following activities:
    - ♦ Review of body systems and collection of general health status (to be followed up with in-person examination if indicated)
    - ♦ Review of new, and follow-up of existing, adverse events and concomitant medications between regularly scheduled on site visits.
- Please continue to collect PK samples as far as possible
- If study imaging procedures cannot be performed at the active clinical study site, participants will be permitted to use other local imaging facilities (eg, at hospitals that are not the active study site). In these cases, digital copies should be made available to the investigator. Copies of the results should be included in the participant's study chart as a source document. The sponsor's Medical Monitor must be informed if radiographic assessments are delayed.
- If site visits are not feasible, participants may be eligible for home shipments of lazertinib where permitted and deemed feasible. If there is a need to consider shipment of lazertinib to a participant's home, then the site must contact its Site Manager to discuss this option, so that the necessary approvals and arrangements can be put in place, subject to local regulatory guidelines. If required and permissible, shipment of study medication to a participant's home would be the responsibility of the site (due to privacy issues), with support from the sponsor and requires 100% traceability (ie, courier tracking with a signed receipt). Participants continuing oral therapy at home should be monitored remotely on a schedule consistent with the protocol and instructed to hold study treatment in the event of worsening respiratory symptoms and contact their study sites/physicians immediately.
- As SARS-CoV-2 represents a new infectious agent and COVID-19 a new clinical syndrome, it is unclear how infection with this virus, which can cause severe pneumonia, will impact the benefit/risk assessment with regards to lazertinib treatment. In addition, study treatment should be held in all participants with suspected (symptomatic) or documented SARS-CoV-2 positive disease, until recovery from all infection related symptoms, and documented to be negative for SARS-CoV-2. Given the unmet medical need of this study population, and the unknown impact of prior COVID-19 infection on the risk of study treatment, re-initiation of study treatments should be evaluated with the sponsor's Medical Monitor on a case-by-case basis, taking into account the severity of the COVID-19 related symptoms, and the observed

clinical benefit from study treatment. Please report the event to the sponsor, following usual Adverse Event reporting requirements.

- The sponsor's Medical Monitor must be informed of any interruption in lazertinib treatment due to COVID-19
- Any deviations from Protocol 73841937NSC2001 Part D must be well documented and where applicable attributed to COVID-19. In accordance with Health Authority guidance the final Clinical Study Report must include these deviations. Case report forms should capture specific information, including the relationship to the COVID-19 pandemic.
- Monitoring Visits: When on-site monitoring by the sponsor is not feasible due to changes in hospital visitation policies, the sponsor's site monitor will contact the study site to schedule remote visits. In such cases, on-site monitoring visits will resume when feasible, with increased frequency to address the source data verification backlog.

Even with staffing limitations during this COVID-19 pandemic, all routine operations related to clinical trials should be well-documented and archived as part of standard process. When conditions permit, all parties involved in this clinical trial should communicate relevant information so that all relevant parties remain sufficiently informed to take any necessary measures in a timely manner.

INVESTIGATOR AGREEMENT

COVID-19 Appendix
JNJ-73841937 (YH25448) Clinical Protocol 73841937NSC2001

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

Signature: PPD Digitally signed by PPD Reason: I am approving this document. Date: 2020.04.28 14:09:06 -07'00' Adobe Reader version: 11.0.20 Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

CONFIDENTIAL – FOIA Exemptions Apply in U.S. 5
Status: Approved, Date: 28 Apr 2020