An Open-label, Randomized Phase 3 Efficacy Study of ASP8273 vs Erlotinib or Gefitinib in First-line Treatment of Patients with Stage IIIB/IV Non-small Cell Lung Cancer Tumors with EGFR Activating Mutations (SOLAR Study)

ISN/Protocol 8273-CL-0302

ClinicalTrials.gov Identifier: NCT02588261

Date of Protocol: Version 2.0, dated 19 Feb 2016

Sponsor: Astellas Pharma Global Development, Inc. (APGD)

1 Astellas Way

Northbrook, IL 60062

An Open-label, Randomized Phase 3 Efficacy Study of ASP8273 vs Erlotinib or Gefitinib in First-line Treatment of Patients with Stage IIIB/IV Non-small Cell Lung Cancer Tumors with EGFR Activating Mutations

SOLAR Study

Protocol for Phase 3 Study of ASP8273

ISN/Protocol 8273-CL-0302

Version 2.0

Incorporating Substantial Amendment 1 [See Attachment 1]

19 February 2016

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EudraCT 2015-002894-39

Sponsor:

Astellas Pharma Global Development, Inc. (APGD)
1 Astellas Way
Northbrook, IL 60062

Protocol History:
Version 1.0 Original [29Jul2015]

Investigator: Investigator information is on file at Astellas.

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I. SIGNATURES

1. SPONSOR'S SIGNATURE

Required signatures (e.g., protocol authors, sponsor's reviewers and contributors, etc.) are located in [**Section 14. Sponsor's Signatures**; e-signatures (when applicable) are located at the end of this document.

2. COORDINATING INVESTIGATOR'S SIGNATURE

An Open-label, Randomized Phase 3 Efficacy Study of ASP8273 vs Erlotinib or Gefitinib in First-line Treatment of Patients with Stage IIIB/IV Non-small Cell Lung Cancer Tumors with EGFR Activating Mutations

ISN/Protocol 8273-CL-0302

Version 2.0 / Incorporating Substantial Amendment 1

19 February 2016

I have read all pages of this clinical study protocol for which Astellas is the sponsor. I agree that it contains all the information required to conduct this study.

Coordinating Investigator:

Signature: ....

<*Insert name, department/affiliation, name of institution*> Date (DD Mmm YYYY)

Printed Name: .....

Address: .....

.....

3. INVESTIGATOR'S SIGNATURE

An Open-label, Randomized Phase 3 Efficacy Study of ASP8273 vs Erlotinib or Gefitinib in First-line Treatment of Patients with Stage IIIB/IV Non-small Cell Lung Cancer Tumors with EGFR Activating Mutations

ISN/Protocol 8273-CL-0302

Version 2.0 / Incorporating Substantial Amendment 1

19 February 2016

I have read all pages of this clinical study protocol for which Astellas is the sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with ICH GCP guidelines and applicable local regulations. I will also ensure that subinvestigator(s) and other relevant members of my staff have access to copies of this protocol and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents.

Principal Investigator:

Signature: .....

<Insert name and qualifications of the investigator> Date (DD Mmm YYYY)

Printed Name: .....

Address: .....

.....

II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

24h-Contact for Serious Adverse Events (SAEs) **See [Section 5.5.5**	[redacted], MD [redacted] **Astellas Pharma Global Development, Inc.** **Mobile:** [redacted] **Please fax the SAE Worksheet to:** Astellas Pharma Global Development, Inc. [redacted] **For Japan:** [redacted] [redacted] – Japan [redacted]
Medical Monitor: Medical Expert:	[redacted], MD [redacted] [redacted], MD [redacted] Astellas Pharma Global Development, Inc. 1 Astellas Way, Northbrook, Illinois 60062 [redacted]
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Clinical Research Contacts:	Asia-Pacific: [redacted], PhD [redacted] Japan: [redacted]

III. LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
AE	Adverse event
AGP	α-acid glycoprotein
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase (GPT)
ANC	Absolute neutrophil count
AntiHCV	Hepatitis C antibody
APEL	Astellas Pharma Europe Limited
APGD	Astellas Pharma Global Development
APTT	Activated partial thromboplastin time
AREC	Astellas Research Ethics Committee
AST	Aspartate aminotransferase (GOT)
AUC	Area under the concentration – time curve
AUC_{inf}	Area under the concentration – time curve from time 0 extrapolated to infinity
AUC_{last}	Area under the concentration – time curve from time 0 up to the last quantifiable concentration
AUST	Astellas US Technologies
BUN	Blood urea nitrogen
CA	Competent authority
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine phosphokinase
CL/F	Apparent oral systemic clearance
CLtot	Total clearance
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CRM	Continual reassessment method
CRO	Contract research organization
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
eCTD	Electronic Common Technical Document
CV	Coefficient of variation
CYP	Cytochrome P450
CYP3A4	Cytochrome P450 3A4
DCR	Disease control rate
DILI	Drug-induced liver injury
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
eGFR	Estimated glomerular filtration rate
EORTC-QLQ-LC13	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13
EORTC-QLQ-	European Organisation for Research and Treatment of Cancer Core Quality of

Abbreviations	Description of abbreviations
C30	Life Questionnaire
EQ-5D-5L	EuroQol 5-Dimension 5-Level Questionnaire
EU	European Union
FACT-EGFRI-18	Functional Assessment of Cancer Therapy – EGFRI 18 Questionnaire
FAS	Full analysis set
FFPE	Formalin Fixed Paraffin Embedded
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GWAS	Genome-Wide Association Studies
HBsAg	Hepatitis B surface antigen
Hct	Hematocrit
HDL	High density lipoprotein
Hgb	Hemoglobin
HIPAA	Health Insurance Portability And Accountability Act
HIV	Human immunodeficiency virus
HNSTD	Highest nonseverely toxic dose
HR	Hazard ratio
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICR	Imprinting control region
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
ILD	Interstitial lung disease
IMPD	Investigational Medicinal Product Dossier
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IRR	Independent radiologic review
IRT	Interactive Response Technology
ISN	International Study Number
IUD	Intrauterine device
IUS	Intrauterine system
J-NDA	Japan New Drug Application
K_{inact}	Inactivation rate constant
KM	Kaplan-Meier
LA	Latin America
LA-CRF	Liver abnormality case report form
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LFT	Liver function tests
LSO	Last subject out
MAA	Marketing Authorization Application
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDRD	Modification of Diet in Renal Disease

Abbreviations	Description of abbreviations
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NA	North America
NASH	Nonalcoholic steatohepatitis
NCI	National Cancer Institute
NDA	New Drug Application
NOAEL	No observed adverse effect level
NSCLC	Non-small-cell lung cancer
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PDAS	Pharmacodynamic analysis set
PET-CT	Positron emission tomography
PFS	Progression free survival
PFS#1	Disease progression on study drug
PFS#2	Progression free survival on next-line therapy
P-gp	Permeability-glycoprotein
PGx	Pharmacogenomic(s)
PHI	Protected health information
PKAS	Pharmacokinetic analysis set
PPS	Per protocol set
PR	Partial response
PRO	Patient-reported outcome
PT	Prothrombin time
QTcF	Fridericia corrected QT interval
QoL	Quality of life
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SD	Stable disease
SOC	System organ class
SOP	Standard operating procedure
STD_{10}	Severely toxic dose in 10%
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
TLF	Tables, listings and figures
t_{max}	The time after dosing when C_{max} occurs
TNM	TNM Classification of Malignant Tumors
TP	Total protein
ULN	Upper limit of normal
Vss	Steady state volume of distribution
Vz/F	Apparent volume of distribution
WBC	White blood cell
WHO	World Health Organization

Definition of Key Study Terms

Terms	Definition of terms
Baseline	Observed values/findings which are regarded observed starting point for comparison.
Enroll	To register or enter into a clinical trial. NOTE: Once a subject has been enrolled, the clinical trial protocol applies to the subject.
Intervention	The drug, therapy or process under investigation in a clinical study that is believed to have an effect on outcomes of interest in a study. (e.g., health-related quality of life, efficacy, safety, pharmacoeconomics).
Investigational period	Period of time where major interests of protocol objectives are observed, and where the test drug or comparative drug (sometimes without randomization) is usually given to a subject, and continues until the last assessment after completing administration of the test drug or comparative drug.
Post investigational period	Period of time after the last assessment of the protocol. Follow-up observations for sustained adverse events and/or survival are done in this period.
Screening period	Period of time before entering the investigational period, usually from the time of starting a subject signing consent until just before the test drug or comparative drug (sometimes without randomization) is given to a subject.
Randomization	The process of assigning trial subjects to treatment or control groups using an element of chance to determine assignments in order to reduce bias.
Screening	A process of active consideration of potential subjects for enrollment in a trial.
Screen failure	Potential subject who did not meet 1 or more criteria required for participation in a trial.
Study period	Period of time from the first site initiation date to the last site completing the study.
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

IV. SYNOPSIS

Date and Version No of Protocol Synopsis:	19 February 2016 / Version 2.0
Sponsor: Astellas Pharma Global Development Inc. (APGD)	**Protocol Number:** 8273-CL-0302
Name of Study Drug: ASP8273	**Phase of Development:** 3

Title of Study:
An Open-label, Randomized Phase 3 Efficacy Study of ASP8273 vs Erlotinib or Gefitinib in First-line Treatment of Patients with Stage IIIB/IV Non-small Cell Lung Cancer Tumors with EGFR Activating Mutations

Planned Study Period:
4Q2015 to 4Q2018

Study Objective(s):

Primary

- To evaluate the progression free survival (PFS), based on independent radiologic review (IRR), of ASP8273 compared to erlotinib or gefitinib in patients with locally advanced, metastatic or unresectable stage IIIB/IV adenocarcinoma non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) activating mutations

Secondary

- Overall survival (OS)
- Overall response rate (ORR) as assessed by IRR
- PFS as assessed by the investigator
- Disease control rate (DCR) as assessed by IRR
- Duration of Response (DOR) as assessed by IRR
- Safety of ASP8273
- To evaluate Quality of Life (QoL) and patient-reported outcome (PRO) parameters as measured by FACT-EGFRI-18, EORTC-QLQ-LC13, EORTC-QLQ-C30 and EQ-5D-5L

Exploratory

- To evaluate potential biomarkers that may affect treatment outcome
- Evaluation of the pharmacokinetics of ASP8273
- To evaluate the impact of subsequent therapy on progression free survival on next-line therapy (PFS#2)

Planned Total Number of Study Centers and Location(s):
Approximately 240 centers (Globally)

Study Population:
Subjects with locally advanced, metastatic or unresectable Stage IIIB/IV adenocarcinoma NSCLC with EGFR activating mutations (exon 19 deletion or exon 21 L858R), with or without a T790M mutation, who have not previously been treated with an EGFR inhibitor (1st line).

Number of Subjects to be Enrolled/Randomized:
Approximately 600 subjects

Study Design Overview:

This multinational, open-label randomized study will evaluate ASP8273 compared to erlotinib or gefitinib (1st generation EGFR tyrosine kinase inhibitor [TKI]) as first line therapy in subjects with locally advanced, metastatic or unresectable stage IIIB/IV adenocarcinoma NSCLC (newly diagnosed or recurrent) with EGFR activating mutations (exon 19 deletion or exon 21 L858R), with or without a T790M mutation, who have not previously been treated with an EGFR inhibitor (1st line).

PFS by IRR is the primary variable. Secondary variables include OS, ORR, PFS by the investigator, DCR, DOR, safety and QoL/PRO. Exploratory variables include biomarkers, pharmacokinetics and PFS #2 on subsequent therapy.

Approximately 600 subjects will be randomized 1:1 to 1 of 2 treatment arms (Arm A or Arm B). Arm A will receive 300 mg daily of ASP8273 and Arm B will receive either 150 mg erlotinib or 250 mg gefitinib daily, as decided by the investigator for each site at the beginning of the trial. Both arms will follow 28-day cycles of continuous dosing. Subjects will be stratified according to the following: ECOG PS (0, 1 or 2), EGFR mutation status (exon 19 deletion or mutations in exon 21 [L858R]), TKI chosen (erlotinib or gefitinib) and race (Asian versus non-Asian).

Screening will take place up to 28 days prior to subject randomization on cycle 1 day 1. Subjects will start with cycle 1 and continue on to subsequent 28-day cycles until 1 of the discontinuation criteria are met. Subjects will visit the clinic for evaluations on day 1 and day 15 of treatment cycle 1 and then on day 1 of subsequent treatment cycles up to cycle 7. Subjects who continue past cycle 7 will have visits on day 1 of each odd-numbered cycle.

Quality of life will be assessed during each treatment cycle where a visit takes place, at the follow-up visit, and at each of the posttreatment or long-term follow-up survival contacts for 6 months after treatment discontinuation (EQ-5D-5L only).

Imaging will be evaluated at baseline and every 56 days (± 7 days) throughout the study. Imaging of the brain is required at baseline for all subjects, and may be repeated throughout the study as clinically indicated. If a brain lesion not previously irradiated is selected as a target lesion at baseline, the assessment should be repeated at all subsequent imaging timepoints. A blinded independent central reader will review all imaging scans to confirm complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) per Response Evaluation Criteria in Solid Tumors (RECIST) V1.1. Disease progression on study drug (PFS#1) should be confirmed by the blinded independent central reader before subjects are discontinued from treatment.

Following discontinuation from study drug, subjects will have a follow-up visit 30 days (+ 7 days) after their last dose of drug for safety assessments. If a subject discontinues study drug prior to radiographic disease progression (i.e., PFS#1), the subject should enter the posttreatment follow-up period and continue to undergo imaging assessments every 56 days (±7 days) until PFS#1 is documented or the subject starts another anticancer treatment, whichever occurs earlier.

Following PFS#1, subjects will enter the long-term follow-up period and be followed every 3 months from the date of the follow-up visit for survival status and progression status on subsequent therapy (i.e., PFS #2). Subjects will be followed until PFS#2 is documented or the subject starts another anticancer treatment, whichever occurs earlier. All subsequent anticancer therapy including date and site of progression for PFS#2 will be recorded on the case report form. Following PFS#2, subjects will enter the survival follow-up period and be followed every 3 months for survival status.

Samples for pharmacokinetics, biomarkers and pharmacogenomics (PGx) as well as formalin fixed paraffin embedded (FFPE) specimens for central analysis will be collected. Eligibility may be determined by a previously documented EGFR mutation result. However, there should be sufficient tissue from the specimen used to generate the EGFR test result to send to the central lab for confirmatory testing. If a subject does not have a previously documented EGFR mutation test result, then a fresh specimen must be obtained and sent to the central lab for eligibility testing. An optional

post-progression tumor tissue sample for exploratory analysis of biomarkers (e.g., EGFR mutation [T790M, C797S], c-Met mutation/amplification and AXL over expression) which are potentially related to EGFR-TKI drug response or resistance may be collected following locally or centrally confirmed disease progression for subjects who sign a separate informed consent form (ICF).

An independent Data Monitoring Committee (IDMC) will be chartered to oversee safety and the planned interim futility analysis which will occur after at least 210 PFS#1 events have been observed.

The primary analysis will occur when at least 420 PFS#1 events are observed which is expected to occur approximately 36 months after randomization of the first subject. Primary endpoint, secondary endpoints and other endpoints will be analyzed at the time of primary analysis.

Inclusion/Exclusion Criteria:

Inclusion Criteria

Subject must meet all of the following inclusion criteria to be eligible for participation in this study at enrollment:

1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written informed consent and privacy language as per national regulations (e.g., HIPAA Authorization for U.S. sites) must be obtained from the subject or legally authorized representative prior to any study-related procedures.
2. Subject is ≥ 18 years of age and legally an adult according to local regulation at the time of signing informed consent.
3. Subject agrees not to participate in another interventional study while on treatment.
4. Female subject must either:
   - Be of nonchildbearing potential:
     - postmenopausal (defined as at least 1 year without any menses) prior to Screening, or
     - documented surgically sterile
   - Or, if of childbearing potential:
     - Agree not to try to become pregnant during the study and for 28 days after the final study drug administration
     - And have a negative serum pregnancy test at Screening
     - And, if heterosexually active, agree to consistently use 2 forms of birth control* (at least 1 of which must be a highly effective method* and one must be a barrier method) starting at Screening and throughout the study period and for 28 days after the final study drug administration
5. Female subject must not be breastfeeding at Screening or during the study period, and for 28 days after the final study drug administration.
6. Female subject must not donate ova starting at Screening and throughout the study period, and for 28 days after the final study drug administration.
7. Male subject and their female spouse/partners who are of childbearing potential must be using highly effective contraception consisting of 2 forms of birth control* (1 of which must be a barrier method) starting at Screening and continue throughout the study period and for 90 days after the final study drug administration.

   *Highly effective forms of birth control include:
   - Consistent and correct usage of established oral, injected or implanted hormonal methods of contraception
   - Established intrauterine device (IUD) or intrauterine system (IUS)

   *Acceptable forms of birth control include:
   - Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository (not applicable in Japan and Thailand: with spermicidal foam/gel/film/cream/suppository)

- Calendar-based contraceptive methods (Knaus-Ogino or rhythm method [Japan and Thailand only])

8. Male subject must not donate sperm starting at Screening and throughout the study period and for 90 days after the final study drug administration.
9. Subject has Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.
10. Subject has histologically confirmed locally advanced, metastatic or unresectable Stage IIIB/IV adenocarcinoma NSCLC (newly diagnosed or recurrent). Subjects with mixed histology are eligible if adenocarcinoma is the predominant histology.
11. Subject has predicted life expectancy ≥ 12 weeks in the opinion of the investigator.
12. Subject must meet all of the following criteria on the laboratory tests that will be analyzed centrally within 7 days prior to the first dose of study drug. In case of multiple laboratory data within this period, the most recent data should be used.
    - Neutrophil count > 1,000/mm^3
    - Platelet count ≥ 7.5×10^4 /mm^3
    - Hemoglobin > 8.0 g/dL
    - Serum creatinine < 2.0 x upper limit of normal (ULN) or an estimated glomerular filtration rate (eGFR) of > 50 mL/min as calculated by the Cockcroft Gault Method
    - Total bilirubin < 1.5 × ULN (except for subjects with documented Gilbert's syndrome)
    - AST and ALT < 3.0 × ULN or ≤ 5 × ULN if subject has documented liver metastases
    - Serum sodium level is ≥ 130 mmol/L
13. Subject has an EGFR activating mutation (exon 19 deletion or exon 21 L858R), with or without T790M mutation, by local or central testing on examination of a NSCLC FFPE specimen (archival or fresh biopsy). Subjects harboring both exon 19 deletion and exon 21 L858R mutations are not eligible. A tissue sample from the same block used to determine eligibility by local testing should be available to send to the central lab for confirmatory testing. Subjects randomized based on local results indicating presence of EGFR mutation may remain on study if central results are discordant.
14. Subject must have at least 1 measureable lesion based on RECIST V1.1. Previously irradiated lesions will not be considered as measurable lesions.

Exclusion Criteria

Subject who meets any of the following exclusion criteria prior to enrollment is not eligible for enrollment:

1. Subject has received intervening anticancer treatment or previous treatment with chemotherapy for metastatic disease other than palliative local radiation to painful bone metastases completed at least 1 week prior to the first dose of study drug. The administration of neoadjuvant or adjuvant chemotherapy is allowed as long as it has finalized ≥ 6 months before the first dose of study drug.
2. Subject has received a prior treatment with a therapeutic agent targeting EGFR (e.g., afatinib, dacomitinib, ASP8273, etc).
3. Subject has received investigational therapy within 28 days or 5 half-lives prior to the first dose of study drug.
4. Subject has received radiotherapy within 1 week prior to the first dose of study drug. If the subject received radiotherapy > 1 week prior to study treatment, the irradiated lesion cannot be the only lesion used for evaluating response.

5. Subject has symptomatic central nervous system (CNS) metastasis. Subject with previously treated brain or CNS metastases are eligible provided that the subject has recovered from any acute effects of radiotherapy, does not have brain metastasis related symptoms, is not requiring systemic steroids for at least 2 weeks prior to study drug administration, and any whole brain radiation therapy was completed at least 4 weeks prior to study drug administration or any stereotactic radiosurgery (SRS) was completed at least 2 weeks prior to study drug administration. Steroid inhaler use or ointment treatment for other concomitant medical disease is permitted.
6. Subject has received blood transfusions or hematopoietic factor therapy within 14 days prior to the first dose of study drug.
7. Subject has had a major surgical procedure (other than a biopsy) within 14 days prior to the first dose of study drug, or one is planned during the course of the study.
8. Subject has a known history of a positive test for human immunodeficiency virus (HIV) infection.
9. Subject has known history of serious hypersensitivity reaction to a known ingredient of ASP8273, erlotinib or gefitinib.
10. Subject has evidence of an active infection requiring systemic therapy within 14 days prior to the planned first dose of study drug.
11. Subject has severe or uncontrolled systemic diseases including uncontrolled hypertension (blood pressure > 150/100 mmHg) or active bleeding diatheses.
12. Subject has history of drug-induced interstitial lung disease (ILD) or any evidence of active ILD.
13. Subject has ongoing cardiac arrhythmia that is Grade ≥ 2 or uncontrolled atrial fibrillation of any grade.
14. Subject currently has Class 3 or 4 New York Heart Association congestive heart failure.
15. Subject has history of severe/unstable angina, myocardial infarction or cerebrovascular accident within 6 months prior to the planned first dose of study drug.
16. Subject has history of gastrointestinal ulcer or gastrointestinal bleeding within 3 months prior to the planned first dose of study drug.
17. Subject has concurrent corneal disorder or any ophthalmologic condition which, in the investigator's opinion, makes the subject unsuitable for study participation (i.e., advanced cataracts, glaucoma).
18. Subject has difficulty taking oral medication or any digestive tract dysfunction or inflammatory bowel disease that would interfere with the intestinal absorption of drug.
19. Subject has another past or active malignancy which requires treatment. Prior carcinoma in situ or non-melanoma skin cancer after curative resection are permitted.
20. Subject has any condition which, in the investigator's opinion, makes the subject unsuitable for study participation.
21. Subject has received potent CYP 3A4 inhibitors within 7 days prior to first dose of study drug or proton pump inhibitors such as omeprazole within 14 days prior to first dose of study drug.

Investigational Product(s):

ASP8273 100 mg capsule strength

Dose(s):

The dose is 300 mg once daily

Mode of Administration:

ASP8273 will be orally administered once daily, at approximately the same time every day on an empty stomach defined as no food for at least 2 hours before and 1 hour after dosing. Concomitant medications should not be administered within 2 hours before or after dosing with ASP8273.

Comparative Drug(s):
Erlotinib/Gefitinib

Dose(s):
Erlotinib 150 mg once daily or gefitinib 250 mg once daily as decided by the investigator for each site at the beginning of the trial.

Mode of Administration:
Erlotinib will be taken orally, at approximately the same time every day on an empty stomach defined as no food for at least 2 hours before and 1 hour after dosing.

Gefitinib will be taken orally, with or without food, at approximately the same time every day.

Concomitant medications should not be administered within 2 hours before or after dosing with erlotinib or gefitinib.

Dose Modifications:
Dosing for ASP8273, erlotinib or gefitinib may be interrupted or reduced (ASP8273 and erlotinib only) for any event if the investigator deems it necessary to ensure subject safety. Subjects requiring a treatment interruption should be re-evaluated not longer than 7 days from initial interruption and restarted on study drug as soon as clinically stable. The subject may be discontinued from treatment if there is an interruption of treatment for > 14 consecutive days despite optimal treatment of side effects. A discussion with the Medical Monitor should occur to confirm if the subject should continue on study treatment.

In the event of acute onset or worsening of pulmonary symptoms likely suggestive of ILD (dyspnea, cough, fever), study drug should be interrupted and a prompt investigation of these symptoms should occur and appropriate treatment initiated. If ILD is confirmed, study drug should be discontinued, and the subject should be treated appropriately per local standard of care.

Study drug should be interrupted if the subject experiences eye toxicity such as acute and severe eye pain or keratitis. Subjects with suspected keratitis should have study drug withheld until recovery and discontinued for persistent severe keratitis. Subjects with ocular toxicities should be evaluated by an ophthalmologist.

If the subject experiences severe hepatic impairment, study drug should be discontinued and the subject should be treated appropriately per local standard of care.

The table below summarizes ASP8273 dose modifications:

Dose level	ASP8273 dose (mg qd)
Starting dose	300
-1	200
-2	100

Subjects requiring a dose reduction may be re-escalated one dose level (i.e., subjects reduced to 100 mg may only be re-escalated to 200 mg). If the event leading to the reduction recurs, the subject should be reduced the lower dose level and not re-escalated again. If a grade 3 or 4 study drug-related toxicity persists or recurs after 2 dose reductions, the subject should be permanently discontinued from ASP8273 treatment. Additionally, if after resolution of a Grade 4 event requiring dose interruption and/or dose reduction, the event reoccurs at a G3 or higher the subject should be permanently discontinued from ASP8273.

Please refer to Section 5.1.2 of the protocol for detailed dose modification criteria.

The table below summarizes Erlotinib dose modifications:

Dose level	Erlotinib (mg qd)
Starting dose	150
-1	100
-2	50

Dose modifications for erlotinib are suggested for toxicities of ILD, skin rash, and diarrhea, however, the locally approved label for erlotinib dose modification for toxicities should be followed. Subjects requiring dose reduction of erlotinib may have the dose re-escalated if they have been on a stable dose for ≥ 3 weeks without further toxicities requiring dose modification and it is considered by the investigator to be in the best interest of the subject. If any toxicity requiring dose interruption of erlotinib recurs despite the initial dose reduction to level -1 (100 mg qd), erlotinib may be reduced again to level -2 (50 mg qd). If 2 levels of erlotinib dose reduction are required, subsequent reescalation may only be to dose level -1.

Please refer to section 5.1.2 of the protocol for detailed dose modification criteria.

Recommended therapy interruption for gefitinib is provided, however, the locally approved label for gefitinib dose interruption should be followed. There will be no dose reductions for subjects receiving gefitinib, as it is only available as single strength tablet.

Please refer to section 5.1.2 of the protocol for detailed dose modification criteria.

Discontinuation Criteria

A discontinuation is a subject who enrolled in the study and for whom study treatment is permanently discontinued for any reason. The subject is free to withdraw from the study treatment and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

The subject will be discontinued from the treatment period if any of the following occur:

- Subject develops radiological progressive disease (i.e., PFS#1) per RECIST v1.1 based on central confirmation of investigator assessment
    - If there is radiographic evidence of PD by investigator, however the investigator believes the subject is continuing to derive clinical benefit (asymptomatic and/or without worsening of performance status or overall health) from study drug, and an increase in tumor burden is not likely to affect vital organ function, the subject may remain on study drug until the next scheduled radiographic assessment which should occur after 56 days (± 7 days).
    - If the next radiographic assessment indicates PD per RECIST 1.1 which is confirmed by the central reviewer, then the subject must be discontinued from study drug.
    - In the rare event where PD suspected on initial assessment is not confirmed on subsequent scan by the investigator or central reviewer, the subject may continue in the study.
    - The investigator should make every effort to immediately submit radiographic assessments for central review when PD is either suspected or confirmed or uncertainty exists.
    - In case of PD determination by the investigator, however not confirmed by the central reviewer, and subject is progressing clinically and requires new anti-cancer treatment immediately, the subject should be discontinued.
- Subject is required to receive local or systemic anti-cancer treatment based on investigator's clinical opinion.
- Subject develops unacceptable toxicity
- Female subject becomes pregnant
- Investigator decides it is in the subject's best interest to discontinue including clinical progression
- Requirement for significant surgical procedure; however, if surgical procedure is for the resection of the primary or metastatic lesion, the subject may be eligible to continue on study treatment after discussion with the Medical Monitor

- Significant deviation from the protocol or eligibility criteria
- Subject declines further treatment
- Subject is noncompliant with the protocol based on the investigator or Medical Monitor assessment
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject
- Death

Subjects who discontinue study drug and enter the posttreatment follow-up period prior to reaching PFS#1 will be discontinued from the posttreatment follow-up period if any of the following occur:

- Subject develops radiological progressive disease (i.e., PFS#1) based on investigator assessment
- Subject initiates a new systemic anticancer treatment
- Subject misses 2 consecutive scheduled tumor assessments

The subject will be discontinued from the long-term follow-up period (for PFS#2) if any of the following occur:

- Subject initiates a new systemic anticancer treatment (3^{rd} line)
- Subject exhibits evidence of PD from 2^{nd} line therapy based on investigator assessment
- Subject declines further study participation (i.e., withdraws consent)
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject
- Subject misses 2 consecutive scheduled tumor assessments
- Death
- Sponsor ends long-term follow-up collection period

The subject will be discontinued from the survival follow-up period if any of the following occur:

- Subject declines further study participation (i.e., withdraws consent)
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject
- Death
- Sponsor ends survival follow-up period

Concomitant Medication Restrictions or Requirements:

Arm A (ASP8273)

The following medications/food are likely to influence evaluation of the safety, pharmacokinetics, or efficacy of ASP8273, and will be strictly prohibited:

- Chemotherapy, radiotherapy, immunotherapy, or other medications intended for antitumor activity
- Investigational products or therapy other than ASP8273
- Potent inhibitors (e.g., ketoconazole, grapefruit or grapefruit juice) or inducers (e.g., rifampin, phenytoin or St. John's wort) of CYP3A4
- CYP3A4 and/or P-gp substrates with a narrow therapeutic index

The use of the following medications should be avoided or used with caution and close monitoring:

- Moderate/weak inhibitors or inducers of CYP3A4
- Inhibitors or inducers of P-gp
- CYP3A4 and/or P-gp substrates

Arm B (Erlotinib/Gefitinib)

The following medications/food are likely to influence evaluation of the safety, pharmacokinetics, or efficacy of erlotinib/gefitinib, and will be strictly prohibited:

- Chemotherapy, radiotherapy, immunotherapy, or other medications intended for antitumor activity other than erlotinib/gefitinib
- Investigational products or therapy
- Potent inhibitors (e.g., ketoconazole, grapefruit or grapefruit juice) or inducers (e.g., rifampin, phenytoin or St. John's wort) of CYP3A4
- Proton pump inhibitors or drugs that cause significant elevation in gastric pH

The use of the following medications should be avoided or used with caution and close monitoring while the subject is receiving erlotinib/gefitinib:

- Moderate/weak inhibitors or inducers of CYP3A4
- Inhibitors or inducers of P-gp
- Warfarin
- For subjects who are randomized to erlotinib:
  - Potent inhibitors of CYP1A2
- For subjects who are randomized to gefitinib:
  - Potent inhibitors of CYP2D6
  - CYP2D6 substrates with narrow therapeutic index

Duration of Treatment:

Subjects will be allowed to receive ASP8273 or erlotinib/gefitinib until discontinuation criteria are met.

Endpoints for Evaluation:

Primary

- PFS as assessed by IRR

Secondary

- OS
- Best overall response rate (CR + PR) by IRR
- PFS by the investigator
- DCR (CR+PR+SD) by IRR
- DOR by IRR
- Safety variables (e.g., adverse events [AEs], laboratory tests, vital sign measurements, electrocardiograms [ECGs])
- QoL and PRO parameters as measured by FACT-EGFRI-18, EORTC-QLQ-LC13, EORTC-QLQ-C30 and EQ-5D-5L

Exploratory

- Plasma T790M and other biomarkers related to EGFR TKI sensitivity and/or resistance
- Plasma pharmacokinetics of ASP8273
- PFS#2 on subsequent therapy

Biomarkers:

Tumor tissue sample (FFPE) will be obtained and sent for central confirmatory testing to evaluate for EGFR activating mutation. The sample sent for confirmatory testing should be from the same specimen as used for local testing for eligibility. A plasma sample will be collected to evaluate EGFR mutations. Plasma and whole blood samples will be collected for exploratory analysis of biomarkers (e.g. EGFR mutation [T790M, C797S], c-Met mutation/amplification, AXL over expression) which are potentially related to EGFR-TKI drug response or resistance. An optional post-progression tumor tissue sample for exploratory analysis of biomarkers (e.g., EGFR mutation [T790M, C797S], c-Met mutation/amplification, and AXL over expression) which are potentially related to EGFR-TKI drug

response or resistance may be collected following locally or centrally confirmed disease progression for subjects who sign a separate ICF.

Statistical Methods:

Sample Size Justification:

Approximately 600 subjects will be randomized in a 1:1 ratio to 2 treatment arms: Arm A (ASP8273) and Arm B (erlotinib or gefitinib, as decided by the investigator).

Randomization will be stratified by:

- ECOG PS: 0,1 or 2
- EGFR mutation status: exon 19 deletion or mutation in exon 21 [L858R]
- TKI chosen (erlotinib or gefitinib)
- Race (Asian vs nonAsian)

Assuming HR=0.667 (median PFS in Arm A and Arm B are 15.6 months and 10.4 months, respectively), 420 PFS events will provide approximately 98.7% power. The type I error is controlled at 1-sided 0.025.

Safety:

The frequency of AEs and the serious AEs will be summarized by system organ class (SOC) and preferred term. In addition, summary statistics will be provided for the following safety parameters:

- Laboratory values
- Vital sign measurements
- ECGs
- ECOG Performance status

Efficacy:

The Full Analysis Set (FAS) will be used for the primary efficacy analysis. All subjects who are randomized will be included in the FAS. For time to event endpoints including PFS, OS and DOR, log-rank test stratified by ECOG PS (0 and 1 combined versus 2), EGFR mutation status (exon 19 deletion or mutations in exon 21 [L858R]), TKI chosen (erlotinib versus gefitinib) will be used to compare the 2 treatment arms. The hazard ratio and corresponding 95% confidence interval from the stratified Cox proportional hazards regression model will also be presented. The median survival function will be estimated using the Kaplan-Meier method and will be reported along with the corresponding 95% confidence interval by treatment arm.

ORR and DCR will be compared between treatment arms using Cochran-Mantel-Haenszel test, stratified by the same stratification factors used in time to event analyses. The difference in response rates between the treatment arms will be estimated along with the corresponding 95% confidence interval.

Hochberg procedure will be used to control the overall error rate at 1-sided 0.025 level for secondary efficacy endpoints (OS and ORR). Only when the primary endpoint significantly favors the ASP8273 arm will secondary endpoints be tested.

Pharmacokinetics:

Descriptive statistics (e.g., N, mean, standard deviation, minimum, median, maximum, coefficient of variation and geometric mean) will be provided for plasma concentrations of ASP8273 and its metabolite(s) (if applicable) at each visit. Additional model-based analyses may be performed and reported separately.

Interim Analyses:

An interim futility analysis is planned to occur after at least 210 PFS events are observed, which is expected approximately 22 months after the first subject is randomized. If the observed HR at the

interim is larger than 1.1, recruitment into the study may be stopped at the interim analysis. Otherwise, recruitment into the study will continue as planned until 600 subjects are recruited. The interim analysis will be conducted by the IDMC. In addition safety data reviews during the trial will be conducted by the IDMC on a periodic basis. For example, the IDMC will review safety data after the first 50 subjects have been randomized and on study drug for approximately 3 months. The full procedures for IDMC safety review will be described in a separate IDMC charter.

V. FLOW CHART AND SCHEDULE OF ASSESSMENTS

Flow Chart

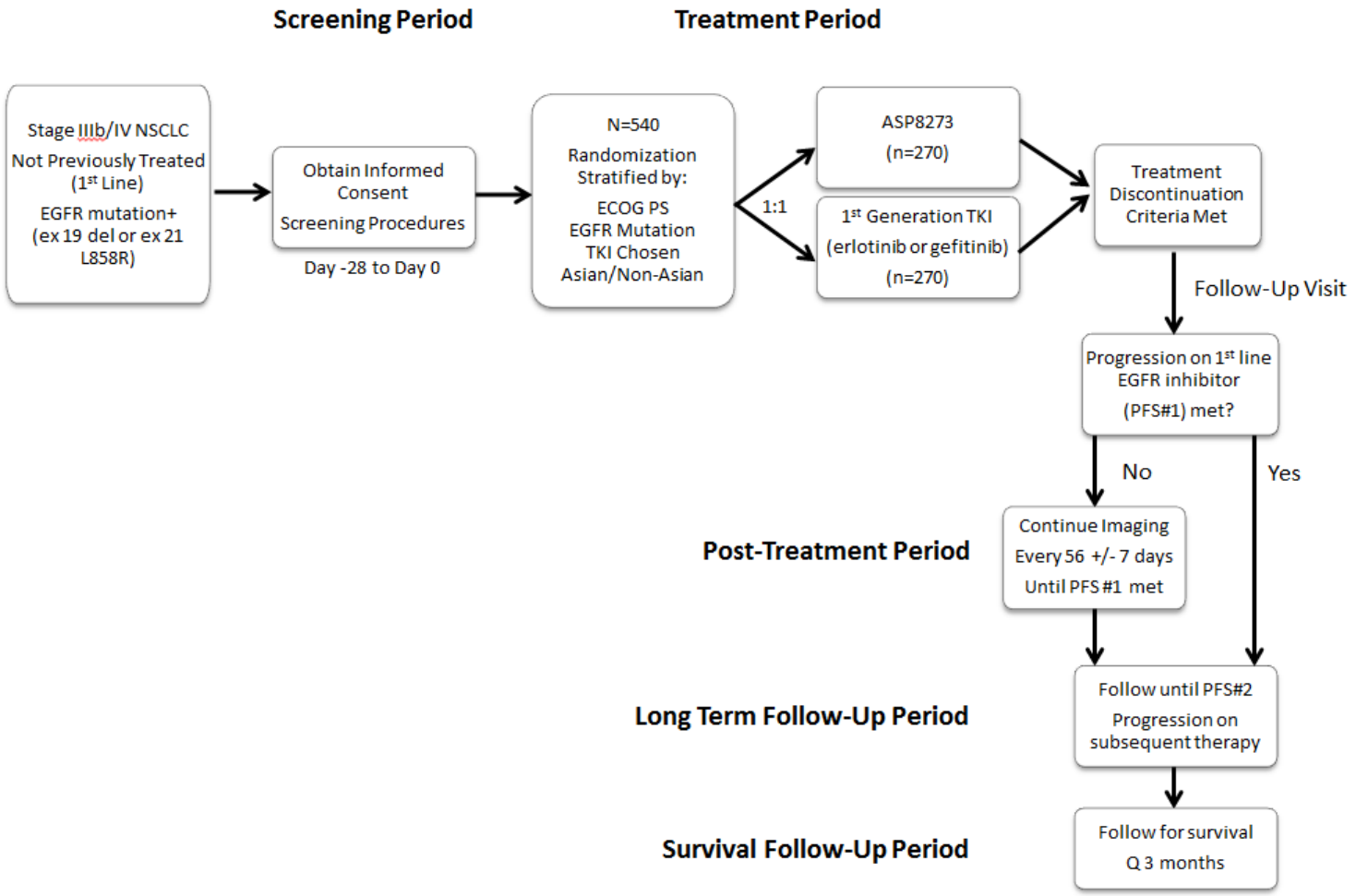


Table 1 Schedule of Assessments

VISIT	Screening	Cycle 1		Cycle 2	Cycle 3-6	≥ Cycle 7 (odd cycles)	End of Treatment
Base Date		Day 1	Day 15	Day 1	Day 1	Day 1	Date of Last Dose
Visit Window	Day -28 to 0		±1 day	±3 days	±7 days	±7 days	+7 days
Informed Consent	X						
Medical and Disease History	X						
Confirmation of Eligibility	X	X					
Randomization[1]		X					
Study Drug Administration[2]		X	X	X	X	X	
Physical Examination [3]	X	X		X	X	X	X
ECOG PS	X	X		X	X	X	X
Vital Signs	X	X	X	X	X	X	X
Biochemistry[4]	X	X	X	X	X	X	X
Hematology[5]	X	X	X	X	X	X	X
Coagulation Parameters[6]		X		X	X	X	X
Urinalysis[7]		X	X	X	X	X	X
Serum Pregnancy Test[8]	X	X		X	X	X	X
12-lead ECG[9]	X	X	X	X	X	X	X
Image Assessment[10]	X				X	X	
Tumor Sample – EGFR[11]	X						
Post-progression Tumor Sample (optional)[12]							X
Plasma Sample – EGFR	X						X
Pharmacokinetics – Blood[13]			X	X	X	X	X
Plasma Sample –Biomarkers[14]		X			X	X	X
Whole Blood Sample – Biomarkers		X					
Whole Blood Sample for PGx (optional)		X					

Table continued on next page

VISIT	Screening	Cycle 1		Cycle 2	Cycle 3-6	≥ Cycle 7 (odd cycles)	End of Treatment
Base Date		Day 1	Day 15	Day 1	Day 1	Day 1	Date of Last Dose
Concomitant Medication	X	X	X	X	X	X	X
Adverse Event	X	X	X	X	X	X	X
Quality of Life (QoL)[15]	X	X		X	X	X	X
Survival Assessment	X	X	X	X	X	X	X

[1] May be performed prior to C1D1 with prior sponsor approval

[2] Daily dosing, 28 days per cycle

[3] Physical examination and other evaluations include height (at screening only) weight, ECOG PS, and vital signs (pulse and blood pressure). Vital signs should be taken predose on dosing days. The physical exam only needs to be repeated on cycle 1 day 1 if clinically significant changes from Screening (in the opinion of the investigator) are observed.

[4] Biochemistry: See [Appendix 12.11] for list of laboratory assessments. All biochemistry laboratory tests should be conducted after the subject has been fasting for at least 6 hours in order to ensure accurate interpretation of glucose values. Fasting status should be recorded in source documents. Biochemistry tests will be sent to a central laboratory for analysis. Additional assessments may be done centrally or locally to monitor adverse events or as required by dose modification requirements.

[5] Hematology: see [Appendix 12.11] for list of laboratory assessments. Hematology tests will be sent to a central laboratory for analysis,

[6] Coagulation: see [Appendix 12.11] for list of laboratory assessments. Coagulation tests will be taken on day 1 of cycles 1-3 and every odd cycle thereafter (cycles 5, 7, 9 etc.). Coagulation tests will be sent to a central laboratory for analysis.

[7] Urinalysis: see [Appendix 12.11] for list of urinalysis assessments. Urinalysis tests will be sent to a central laboratory for analysis.

[8] For female subjects of child bearing potential only. Serum pregnancy tests every cycle where a visit takes place will be done throughout the study.

[9] ECG time points are: Screening; cycle 1 day 1 predose; cycle 1 day 15 predose; and day 1 predose of cycle 2 and each subsequent cycle where a visit takes place. When collected on the same day, ECG should be collected prior to pharmacokinetic samples.

[10] Image assessments will be done every 56 days (± 7 days), scheduled in a way to allow results to be available for the odd cycle day 1 visit (i.e., prior to cycles 3, 5, 7, 9, etc.). Imaging of the brain is required at baseline for all subjects, and may be repeated throughout the study as clinically indicated. If a brain lesion is selected as a target lesion at baseline, the assessment should be repeated at all subsequent imaging timepoints. CT scan with contrast (chest and abdomen) is the preferred modality for tumor assessment. MRI is acceptable if local standard practice or if CT scans are contraindicated in a subject (e.g., subject is allergic to contrast media). All other RECIST-approved scanning methods such as X-ray are optional. PET-CT scans must use contrast. To ensure comparability, the screening and subsequent assessment of response should be performed using identical techniques. The same method should be employed and assessed by the same individual on each occasion if possible. Imaging assessments, including brain, should utilize the same methods throughout the study. Confirmation scans for CR or PR should be done at the next scheduled assessment. A chest x-ray or other appropriate imaging of the lungs should be performed in addition to specified imaging time points if a subject develops symptoms suggestive of ILD.

Footnotes continued on next page

[11] Eligibility may be determined by a previously documented EGFR mutation test result. However, there should be sufficient tumor tissue from the specimen used to generate the EGFR test result to send to the central lab for confirmatory testing. If a subject does not have a previously documented EGFR mutation test result, then a fresh specimen must be obtained and sent to the central lab for eligibility testing. If slides are submitted, the slides should be freshly cut from the FFPE block within 18 days of sending to the central lab. A plasma sample for EGFR mutation detection will also be collected and submitted to the central laboratory.

[12] For subjects who signed a separate ICF, an optional post-progression tumor sample for exploratory biomarker analysis should be collected following local or central confirmation of disease progression and prior to commencement of subsequent anticancer therapy.

[13] Pharmacokinetic samples of ASP8273 will be taken for subjects randomized to Arm A (ASP8273) at predose on cycle 1 day 15 and predose on day 1 of cycles 2, 3, 5, 9 and 13 and at the End of Treatment visit. The date and time of each blood sample collection will be recorded to the nearest minute. In addition, the date and time of the ASP8273 doses taken on the pharmacokinetic days and the last 2 ASP8273 doses taken prior to each pharmacokinetic day will be recorded to the nearest minute. In the event ASP8273 treatment has been withheld for ≥3 days prior to the timepoint, the PK sample will not be collected.

[14] Plasma samples for biomarkers will be collected at predose on day 1 of each odd cycle (cycles 1, 3, 5, 7, 9 etc.) and at the End of Treatment visit. Whole blood sample for biomarkers will be collected once at baseline.

[15] QoL questionnaires are to be administered on visit days before any other scheduled assessments are conducted and before the disease status is discussed with the subject.

Table 2 Posttreatment Discontinuation Schedule of Assessments

VISIT	Follow-up Visit	Posttreatment Follow-up Period	Long-term Follow-up Period	Survival Follow-up Period
Base Date	**Date of last Dose +30 days**	**Every 56 days**	**Every 3 months**	**Every 3 months**
Visit Window	+7 days	±7 days	±7 days	±7 days
ECOG PS	X			
Vital Signs	X			
Image Assessment		X[1]		
Subsequent therapy assessment[2]	X	X	X	
QoL	X			
QoL – EQ-5D-5L only[3]		X	X	
Survival Assessment	X	X	X	X[4]
Adverse Event	X	X		

[1] If a subject discontinues study drug prior to radiographic disease progression (i.e., PFS#1), the subject should continue to undergo imaging assessment (including brain imaging when indicated and collection of tumor measurements) every 56 days (±7 days) in the posttreatment follow-up period until PFS#1 is documented per the investigator, the subject misses 2 or more consecutive scheduled tumor assessments, or the subject starts another cancer treatment, whichever occurs earlier.

[2] After PFS#1, subjects will be followed in the long-term follow-up period per institutional guidelines, but not less frequently than every 3 months to confirm survival status and collect subsequent anticancer treatment details and progression status until PFS#2 is documented or the subject starts another cancer treatment, whichever occurs earlier. Phone contact with subject is sufficient for follow-up. Additional follow-up contacts may be required per sponsor request for analysis purposes.

[3] Quality of life (EQ-5D-5L only) will be assessed at each of the posttreatment or long-term follow-up survival contacts for 6 months after treatment discontinuation. QoL may be assessed by telephone module if follow-up contact is done by phone.

[4] Subjects will be followed via phone call in the survival follow-up period approximately every 3 months to collect survival status until subject death or study closure. Additional follow-up contacts may be required per sponsor request for analysis purposes.

1 INTRODUCTION

1.1 Background

Lung cancer is a leading cause of cancer death worldwide. Lung cancer accounts for over 1 million mortalities annually and NSCLC accounts for almost 85% of all cases [Esposito et al, 2010; Herbst et al, 2008; Ferlay et al, 2007]. Epidermal growth factor receptor (EGFR) mutations are found in approximately 10% and 30% of NSCLC patients in North American/ European and East Asian countries, respectively [Bell et al, 2005; Shigematsu et al, 2005]. EGFR activating mutations result in increased malignant cell survival, proliferation, invasion, metastatic spread and tumor angiogenesis in NSCLC [Herbst et al, 2008; Mendelsohn & Baselga, 2000; Wells A, 1999]. The 2 most common EGFR mutations are short in frame deletions of exon 19, and a point mutation (CTG to CGG) in exon 21 at nucleotide 2573 resulting in the substitution of leucine for arginine in codon 858 (L858R) [Herbst et al, 2008; Ladanyi & Pao, 2008]. These mutations account for approximately 90% of EGFR mutations in NSCLC [Sharma et al, 2007].

ASP8273 mesilate is a novel, small molecule irreversible tyrosine kinase inhibitor (TKI) that inhibits the kinase activity of EGFR containing the exon 19 deletion (del ex19) or the exon 21 (L858R) substitution activating mutation as well as the T790M resistance mutation with higher potency than wild-type EGFR.

Reversible EGFR TKIs, gefitinib and erlotinib, inhibit the growth of NSCLC cell lines expressing EGFR activating mutations as well as wild-type EGFR. These TKIs have shown antitumor efficacy and prolonged progression free survival (PFS) in NSCLC patients with EGFR activating mutations [Mitsudomi et al, 2012; Rosell et al, 2012; Zhou et al, 2012; Zhou et al, 2011; Maemondo et al, 2010; Mitsudomi et al, 2010; Mok et al, 2009]. The clinical efficacy of gefitinib and erlotinib is limited by the development of acquired drug resistance, which is most commonly caused by a T790M resistance mutation in EGFR. This mutation has been detected in approximately 50% to 60% of clinically resistant patients; therefore, along with activating mutations, the T790M mutation is an important factor in treating NSCLC [Ohashi et al, 2013; Kobayashi et al, 2005; Pao et al, 2005].

In this study, ASP8273 will be studied first line in subjects who have EGFR activating mutations and have not been exposed to prior TKI therapy.

Given that in addition to having a high potency to target T790M resistance mutations, ASP8273 mesilate also inhibits several other kinases (BLK, BMX, BTK, FLT3, HER4, ITK, JAK3, TEC, TNK1 and TXK). Therefore, it is thought that treating first line subjects who have EGFR activating mutations with ASP8273 will delay the time to acquiring T790M resistance, resulting in a longer duration of PFS than gefitinib and erlotinib in a first line setting.

This is supported by the fact that ASP8273 mesilate has been shown to inhibit growth of several human NSCLC cell lines harboring EGFR del ex19 or T790M/L858R mutation with higher potency than those with wild-type EGFR. ASP8273 mesilate has induced tumor regression in in vivo tumor models xenografted with NSCLC cell lines harboring EGFR del

ex19 or T790M/L858R mutation. Results from nonclinical studies support the investigation of ASP8273 mesilate in patients with NSCLC, whose tumors harbor EGFR mutations.

1.2 Nonclinical and Clinical Data

1.2.1 Nonclinical Pharmacology

ASP8273 mesilate has been assessed in primary pharmacodynamics studies, as well as in safety pharmacology studies. Tabulated overviews of nonclinical pharmacology studies can be found in the ASP8273 Investigator's Brochure, Version 4 [30 July 2015].

ASP8273 mesilate inhibited the kinase activity of EGFR containing activating mutations, the del ex19 and the exon 21 (L858R) substitution mutation, and also inhibited the kinase activity of EGFR containing both the activating mutation and the T790M resistance mutation (i.e., del ex19/T790M and T790M/L858R). In EGFR mutants (T790M/L858R), ASP8273 mesilate covalently bound to the kinase.

ASP8273 mesilate inhibited growth of HCC827, PC-9 and NCI-H1650 cells, human NSCLC cell lines harboring EGFR del ex19. ASP8273 mesilate also inhibited growth of NCI-H1975 cells, a human NSCLC cell line harboring EGFR mutation T790M/L858R. Antiproliferative activity of ASP8273 mesilate in NCI-H292 and NCI-H1666 cells and human NSCLC cell lines harboring wild-type EGFR, was less potent than in cells harboring EGFR mutations. ASP8273 mesilate inhibited EGFR phosphorylation in NCI-H1975 cells and maintained inhibition for 24 h after washout.

ASP8273 mesilate inhibited tumor growth and induced tumor regression in vivo in mice subcutaneously xenografted with HCC827 or NCI-H1975 cells after 14-day repeat oral administration. ASP8273 mesilate did not affect body weight at any of the doses tested.

1.2.2 Nonclinical Pharmacokinetics

After a single intravenous administration of ASP8273 mesilate at dose levels of 3 mg/kg to rats and 0.3 mg/kg to dogs, plasma concentrations of unchanged ASP8273 decreased with a $t_{1/2}$ of 3.30 and 9.12 h, respectively. The total body clearance (CLtot) and the volume of distribution (Vss) were 1569.4 mL/h per kg and 4906.9 mL/kg in rats, and 1936.2 mL/h per kg and 18946.8 mL/kg in dogs, respectively. After a single oral administration of ASP8273 mesilate at 3, 10 and 30 mg/kg to rats and 0.3, 1 and 3 mg/kg to dogs, the C_{max} and the AUC_{inf} increased more than dose-proportionally. The $t_{1/2}$ ranged from 2.99 to 4.73 h in rats and 9.23 to 9.93 h in dogs. Absolute oral bioavailability (F) was 41.0% in rats and 40.9% in dogs.

After oral administration of a single dose of [^{14}C]ASP8273 mesilate at 10 mg/kg to rats, radioactivity was moderately absorbed and distributed to the tissues. Radioactivity decreased time-dependently in all tissues. Some tissues such as the testes, blood, Harderian glands and thyroid showed relatively slow elimination, with 60.4%, 49.0%, 28.0% and 20.4% of their maximum radioactivity 72 h postadministration, respectively.

The in vitro plasma protein binding ratios of [^{14}C] ASP8273 at concentrations of 0.5, 5 and 50 μg/mL ranged from 89.19% to 91.56% in ICR mice, 87.34% to 93.85% in H1975-xenografted nude mice, 92.07% to 95.37% in rats, 81.10% to 82.97% in rabbits, 76.22% to 81.39% in dogs, 89.13% to 96.94% in monkeys, and 90.89% to 95.91% in humans. Human serum albumin and α_1-acid glycoprotein (AGP) were found to be the primary binding proteins in human plasma.

ASP8273 metabolism by cytochrome P450 (CYP) isozymes was examined using 16 individual human liver microsome samples. Results suggested that CYP3A4/5 is the main CYP isozyme involved in the metabolism of ASP8273. When [^{14}C]ASP8273 mesilate was orally administered to rats at 10 mg/kg, the main component in plasma was the unchanged drug. Species differences in the in vitro metabolic profiles of ASP8273 were investigated with [^{14}C]ASP8273 using pooled liver microsomes and cryopreserved hepatocytes from mice, rats, rabbits, dogs, monkeys and humans. All major metabolite peaks detected in human liver microsomes and cryopreserved hepatocytes were also found in at least 1 other species. No clear sex differences in humans were observed in the metabolic profiles of ASP8273. Structural analysis of in vitro metabolites in humans demonstrated that ASP8273 was mainly metabolized by *N*-demethylation followed by the piperazine cleavage, oxidation and glutathione conjugation.

After oral administration of a single dose of [^{14}C]ASP8273 mesilate at 10 mg/kg to rats, the excretion of radioactivity in urine and feces up to 168 h after dosing was 4.2% and 88.6% of the dose, respectively. The excretion of radioactivity in urine and bile up to 48 h after dosing was 4.0% and 32.4% of the dose, respectively. These results suggest that orally administered ASP8273 mesilate is mainly excreted in feces, with some excretion via the bile. When radioactivity excreted into the bile was injected into the duodenum of other rats, the reabsorption ratio was 0.7%.

ASP8273 showed slight direct inhibition of CYP1A2 and 2C8 (IC_{50} > 300 μmol/L), direct inhibition of CYP2B6, 2C9, 2C19, 2D6, 3A (midazolam) and 3A (testosterone) (IC_{50} values: 152, 30.0, 13.3, 111, 8.33 and 12.5 μmol/L, respectively) as well as possible time-dependent inhibition of CYP3A (midazolam and testosterone). The time-dependent inhibition of CYP3A4 (testosterone) was irreversible, and the in vitro maximum inactivation rate constant (kinact) and inhibitor concentrations that gave half-maximal kinact (Ki) values of ASP8273 were 0.0246 min-1 and 2.12 μmol/L for CYP3A4 (testosterone), respectively. The direct inhibitory effects of ASP8273 on CYP1A2, 2C8, 2B6, 2C9, 2C19 and 2D6 were weak, and may not be clinically relevant.

An in vitro transcellular transport study using permeability-glycoprotein (P-gp)-expressing cells suggested that ASP8273 is a substrate for P-gp-mediated transport. ASP8273 showed an inhibitory effect on P-gp-mediated transport of digoxin with an IC_{50} value of 11.0 μmol/L.

1.2.3 Nonclinical Toxicology

In a single dose toxicity study in rats, the approximate lethal dose level was 500 mg/kg for males and females. The main change noted in moribund animals was gastrointestinal

hemorrhagic disorder. In a preliminary single dose toxicity study in dogs, no animals showed mortality or moribundity up to 300 mg/kg.

In a 4-week once-daily oral dose toxicity study in rats (0, 3, 10, 30 and 60 mg/kg per day), no mortality or moribundity was noted up to 60 mg/kg per day. The main toxicities observed in rats were atrophy of the epithelium in cornea and skin, corneal opacity, atrophy of lymphoid tissues, irreversible testicular atrophy (atrophy and dilatation of the seminiferous tubules, spermatic granuloma in the testes), alveolar foam cells in the lung, multifocal necrosis of hepatocytes, thickening of the epiphyseal cartilage and decreased trabecular bone, and vacuolation and foam cell accumulation observed in multiple organs and tissues. The no observed adverse effect level (NOAEL) in rats was < 3 mg/kg per day, as decreased serum potassium was noted at 3 mg/kg per day or more.

In a 4-week once-daily oral dose toxicity study in dogs (0, 1.5, 5 and 15 mg/kg per day), moribundity was noted at 15 mg/kg per day. Dosing was discontinued after day 20 and day 17 for males and females, respectively. The main organ toxicities in dogs were gastrointestinal injury including vomiting and abnormal stool with occult blood, atrophy of epithelium in cornea and skin, corneal opacity, atrophy of lymphoid tissues, inflammatory cell infiltration, hemorrhage or edema in the alveoli in the lung, dilatation of the distal tubules, focal interstitial hemorrhage, and basophilic changes in the proximal tubules in the kidney, thickening of the epiphyseal cartilage and decreased trabecular bone, and vacuolation and foam cell accumulation observed in multiple organs and tissues. The NOAEL in dogs was < 1.5 mg/kg per day as vomiting, decreased erythrocyte parameters, prolonged activated partial thromboplastin time (APTT), decreased serum albumin and increased alkaline phosphatase (ALP) were observed at doses of ≥ 1.5 mg/kg per day.

Findings in both 4-week studies in rats and dogs were reversible, except for the testicular changes in rats (≥ 10 mg/kg per day) and corneal opacity in rats and dogs (rat: ≥ 30 mg/kg per day, dog: 15 mg/kg per day), which were observed after a 4-week withdrawal period. In the rat, low lymphocyte and basophil counts in peripheral blood were still noted after a 4-week recovery period; however, reversibility of these findings are anticipated because atrophy in the lymphoid organs and bone marrow hypocellularity did recover. Based on these results, the severely toxic dose in 10% of animals (STD10) in rats was considered to be 60 mg/kg per day, and the highest nonseverely toxic dose (HNSTD) in dogs was considered to be 5 mg/kg per day.

In an ongoing 13-week oral dose toxicity study in the rat (0, 0.3, 3, 10 and 30 mg/kg), a male animal from the highest dose group (30 mg/kg) died on day 22 of dosing (8273-TX-0012). The cause of death was considered to be treatment related gastrointestinal damage as has been previously observed in earlier toxicity studies with ASP8273.

In an embryo fetal development toxicity study in rats (0, 3, 10 and 60 mg/kg per day), decreased body weight and food consumption in dams, embryo-fetal death, growth retardation and morphological abnormalities were noted at 60 mg/kg per day. The following morphological abnormalities were noted: a tendency to increase in external malformations, increases in visceral and skeletal malformations, skeletal variations and ossification findings.

The NOAELs were concluded to be 10 mg/kg per day for general toxicity of dams and embryo-fetal development.

ASP8273 mesilate did not show genotoxic potential in an in vitro reverse mutation test in bacteria. Although numerical chromosomal aberrations were induced in an in vitro chromosomal aberration test in mammalian cells, an in vivo micronucleus test in rats at doses up to 500 mg/kg per day showed no potential to induce chromosomal aberrations in vivo.

ASP8273 mesilate showed no potential to induce phototoxicity in cultured mammalian cells.

1.2.4 Clinical Data

ASP8273 mesilate is being evaluated in 3 ongoing studies in NSCLC subjects harboring EGFR activating mutation: phase 1/2 Study 8273-CL-0101 (Japan, Korea and Taiwan), a phase 1 Study 8273-CL-0102 (US), and a phase 2 Study 8273-CL-0202 (Japan). Preliminary pharmacokinetic data from the 2 studies (8273-CL-0101 and 8273-CL-0102) indicated that peak plasma concentrations (C_{max}) of ASP8273 were achieved approximately 1 to 6 hours after a single dose and at steady state. ASP8273 exposure (median AUC and C_{max}) after single and multiple doses increased with dose. At dose levels of 100 mg to 300 mg, ASP8273 exposure was approximately dose-proportional and appeared to be comparable between the 2 studies.

Preliminary data in both ongoing studies noted antitumor activity in the 100 mg and above cohorts; 52.4% (22/42), 73.9% (17/23) and 32.7% (18/55) of patients had a partial response in Studies 8273-CL-0101 (phases 1 and 2) and 8273-CL-0102, respectively. Preliminary safety data is summarized in [Section 1.3.1].

Full details are included in the Investigator's Brochure, Version 4 [30 July 2015].

1.3 Summary of Key Safety Information for Study Drugs

1.3.1 ASP8273

A total of 170 subjects with NSCLC in ongoing Studies 8273-CL-0101 and 8273-CL-0102 have received at least 1 dose of ASP8273 mesilate, with dose ranging from 25 mg to 600 mg (1 subject received a single dose of 800 mg due to overdose). The majority of subjects experienced at least 1 treatment-emergent adverse event (TEAE). In ongoing Study 8273-CL-0101, the 3 most common TEAEs in both studies were diarrhoea, nausea and vomiting; and in ongoing Study 8273-CL-0102, the 4 most common TEAEs were diarrhoea, nausea, constipation and fatigue.

To date, no subject has died due to an adverse event (AE) in ongoing Study 8273-CL-0101. In ongoing Study 8273-CL-0102, 4 subjects experienced TEAEs leading to death (1 subject each experienced respiratory failure [400 mg group], depressed level of consciousness [100 mg group], progression of NSCLC [200 mg group] and multi-organ failure [200 mg group]; all of which were considered not related to ASP8273 mesilate by the investigator.

To date, in ongoing Study 8273-CL-0101, 23 subjects experienced serious AEs (SAEs). Of these, 13 subjects experienced SAEs that were considered possibly or probably related to

study drug. The only drug-related SAEs occurring in more than 1 subject were nausea (4 events), ALT increased (4 events) and hyponatraemia (2 events). In ongoing Study 8273-CL-0102, 19 subjects experienced SAEs. Of these, 3 subjects experienced SAEs that were considered possibly or probably related to study drug (1 event each of nausea [400 mg group], pancreatitis [300 mg], hyponatremia [500 mg group] and urinary retention [500 mg group]).

To date, 2 subjects from Study 8273-CL-0101 (100 and 600 mg group) and 3 subjects (100, 200 and 400 mg group) from Study 8273-CL-0102 permanently discontinued due to a TEAE (primary reason). Nausea, vomiting and hyponatremia were the only drug-related TEAEs resulting in withdrawal of drug.

In ongoing Study 8273-CL-0101, 9 subjects experienced DLTs (400 mg group, n = 5; 600 mg group, n = 4). Diarrhoea was the most common DLT, occurring in 3 subjects. Nausea and colitis each occurred in 2 subjects, while the rest of the DLTs occurred in 1 subject each. In ongoing Study 8273-CL-0102, 3 subjects in the 400 mg group experienced DLTs; they were diarrhea, anorexia and hyponatremia (2 events in 1 subject).

1.3.2 Erlotinib

Detailed information on the toxicities associated with erlotinib can be found within the Package Insert (PI), Summary of Product Characteristics (SPC) or local product information. Special attention should be paid to the prescribing warnings and precautions for use regarding interstitial lung disease (ILD), renal failure, hepatoxocity with or without hepatic impairment, gastrointestinal perforation, bullous and exfoliative skin disorders, myocardial infarction/ischemia, cerebrovascular accident, microangiopathic hemolytic anemia and thrombocytopenia, ocular disorders and embryo-fetal toxicity.

1.3.3 Gefitinib

Detailed information on the toxicities associated with gefitinib can be found within the Package Insert (PI), Summary of Product Characteristics (SPC) or local product information. Special attention should be paid to the prescribing warnings and precautions for use regarding ILD, hepatoxocity and liver impairment, interactions with other medicinal products, lactose, gastrointestinal perforation, keratitis, increased INR in patients taking warfarin, and severe or persistent diarrhea, nausea, or anorexia that may lead to dehydration.

1.4 Risk-Benefit Assessment

ASP8273 has been administered in 2 NSCLC tumor-specific phase 1/2 studies to date. Across these 2 studies preliminary data suggest antitumor activity with ASP8273 in subjects with advanced NSCLC harboring EGFR activating mutations previously treated with an EGFR TKIs, primarily in subjects with known T790M positive mutation status or their mutation status is unknown. This early antitumor activity is consistent with the nonclinical data that suggested that ASP8273 may have antitumor activity in patients with NSCLC harboring EGFR activating mutations with or without the T790M resistance mutation. Hence, this may be a potential benefit for such patients to receive ASP8273.

Additionally, erlotinib and gefitinib are both approved and have demonstrated effectiveness in treating subjects with NSCLC harboring certain activating mutations of EGFR.

The potential undesirable effects in humans based on toxicities observed in the nonclinical studies with ASP8273 are summarized in [Section 1.3]. The most common AEs from the initial safety observations in the 2 ASP8273 phase 1/2 studies to date include diarrhea, nausea, vomiting, constipation and fatigue. The increased frequency and severity of these events appear to occur in a dose dependent manner.

The initial safety observations from these trials are consistent with the preclinical findings and other approved EGFR TKI therapies. Therefore, the possible benefits of antitumor activity in subjects taking ASP8273 therapy appear to outweigh potential risks in this patient population. See the current ASP8273 Investigator's Brochure for full list of TEAEs.

Erlotinib and Gefitinib both have well-characterized safety profiles with acceptable management of AEs in the clinical setting.

The current safety monitoring plan is designed to monitor for EGFR class related toxicities including laboratory values and physical exam findings and contains detailed dose reduction management guidelines specific to these types of AEs. Strict adherence to the schedule of safety assessments to ensure that patients receive adequate safety monitoring is essential. Equally important, strict adherence to the eligibility criteria is essential to ensure that appropriate patients are selected for participation. In addition, an IDMC will be formed to review safety data on a regular basis to ensure patient safety.

The overall risk-benefit assessment for this patient population appears favorable.

2 STUDY OBJECTIVE(S), DESIGN, AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

- To evaluate the progression free survival (PFS), based on independent radiologic review (IRR), of ASP8273 compared to erlotinib or gefitinib in patients with locally advanced, metastatic or unresectable stage IIIB/IV adenocarcinoma non-small cell lung cancer (NSCLC) with EGFR activating mutations

2.1.2 Secondary Objectives

- Overall survival (OS)
- Overall response rate (ORR) as assessed by IRR
- PFS as assessed by the investigator
- Disease control rate (DCR) as assessed by IRR
- Duration of Response (DOR) as assessed by IRR
- Safety of ASP8273
- To evaluate Quality of Life (QoL) and patient-reported outcome (PRO) parameters as measured by FACT-EGFRI-18, EORTC-QLQ-LC13, EORTC-QLQ-C30 and EQ-5D-5L

2.1.3 Exploratory Objectives

- To evaluate potential biomarkers that may affect treatment outcome
- Evaluation of the pharmacokinetics of ASP8273
- To evaluate the impact of subsequent therapy on progression free survival on next-line therapy (PFS#2)

2.2 Study Design and Dose Rationale

2.2.1 Study Design

This multinational, open-label randomized study will evaluate ASP8273 compared to erlotinib or gefitinib (1st generation EGFR TKI) as first line therapy in subjects with locally advanced, metastatic or unresectable stage IIIB/IV adenocarcinoma NSCLC (newly diagnosed or recurrent) with EGFR activating mutations (exon 19 deletion or exon 21 L858R), with or without a T790M mutation, who have not previously been treated with an EGFR inhibitor (1st line).

PFS by IRR is the primary variable. Secondary variables include OS, ORR, PFS by the investigator, DCR, DOR, safety and QoL/PRO. Exploratory variables include biomarkers, pharmacokinetics and PFS#2 on subsequent therapy.

Approximately 600 subjects will be randomized 1:1 to 1 of 2 treatment arms (Arm A or Arm B). Arm A will receive 300 mg daily of ASP8273 and Arm B will receive either 150 mg erlotinib or 250 mg gefitinib daily, as decided by the investigator for each site at the beginning of the trial. Both arms will follow 28-day cycles of continuous dosing. Subjects will be stratified according to the following: ECOG PS (0, 1 or 2), EGFR mutation status (exon 19 deletion or mutations in exon 21 [L858R]), TKI chosen (erlotinib or gefitinib) and race (Asian versus non-Asian).

Screening will take place up to 28 days prior to subject randomization on cycle 1 day 1. Subjects will start with cycle 1 and continue on to subsequent 28-day cycles until 1 of the discontinuation criteria are met. Subjects will visit the clinic for evaluations on day 1 and day 15 of treatment cycle 1 and then on day 1 of subsequent treatment cycles up to cycle 7. Subjects who continue past cycle 7 will have visits on day 1 of each odd-numbered cycle.

Quality of life will be assessed during each treatment cycle where a visit takes place, at the follow-up visit, and at each of the posttreatment or long-term follow-up survival contacts for 6 months after treatment discontinuation (EQ-5D-5L only).

Imaging will be evaluated at baseline and every 56 days (± 7 days) throughout the study. Imaging of the brain is required at baseline for all subjects, and may be repeated throughout the study as clinically indicated. If a brain lesion not previously irradiated is selected as a target lesion at baseline, the assessment should be repeated at all subsequent imaging timepoints. A blinded independent central reader will review all imaging scans to confirm complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) per Response Evaluation Criteria in Solid Tumors (RECIST) V1.1. Disease progression

on study drug (PFS#1) should be confirmed by the blinded independent central reader before subjects are discontinued from treatment.

Following discontinuation from study drug, subjects will have a follow-up visit 30 days (+7 days) after their last dose of drug for safety assessments. If a subject discontinues study drug prior to radiographic disease progression (i.e., PFS#1), the subject should enter the posttreatment follow-up period and continue to undergo imaging assessments every 56 days (+/- 7 days) until PFS#1 is documented or the subject starts another anticancer treatment, whichever occurs earlier.

Following PFS#1, subjects will enter the long-term follow-up period and be followed every 3 months from the date of the follow-up visit for survival status and progression status on subsequent therapy (i.e., PFS#2). Subjects will be followed until PFS#2 is documented or the subject starts another anticancer treatment, whichever occurs earlier. All subsequent anticancer therapy including date and site of progression for PFS#2 will be recorded on the case report form.

Following PFS#2, subjects will enter the survival follow-up period and be followed every 3 months for survival status.

Samples for pharmacokinetics, biomarkers and pharmacogenomics (PGx) as well as formalin fixed paraffin embedded (FFPE) specimens for central analysis will be collected. Eligibility may be determined by a previously documented EGFR mutation result. However, there should be sufficient tissue from the specimen used to generate the EGFR test result to send to the central lab for confirmatory testing. If a subject does not have a previously documented EGFR mutation test result, then a fresh specimen must be obtained and sent to the central lab for eligibility testing. An optional post-progression tumor tissue sample for exploratory analysis of biomarkers (e.g., EGFR mutation [T790M, C797S], c-Met mutation/amplification and AXL over expression), which are potentially related to EGFR-TKI drug response or resistance, may be collected following locally or centrally confirmed disease progression for subjects who sign a separate informed consent form (ICF).

An independent Data Monitoring Committee (IDMC) will be chartered to oversee safety and the planned futility analysis which will occur after at least 210 PFS events have been observed.

The primary analysis will occur when at least 420 PFS#1 events are observed which is expected to occur approximately 36 months after randomization of the first subject. Primary endpoint, secondary endpoints and other endpoints will be analyzed at the time of primary analysis.

2.2.2 Dose Rationale

A once daily treatment of 300 mg has been selected as the recommended starting dose based on the relative balance between antitumor effect and toxicity observed in the phase 1 dose escalation studies (8273-CL-0101 and 8273-CL-0102). Although the 300 mg and 400 mg dose cohorts appear to have comparable preliminary antitumor activity, there were fewer DLTs noted at 300 mg as compared to 400 mg. In the phase 1/2 study in Japan (8273-CL-0101), the MTD for ASP8273 was established as 400 mg utilizing a Bayesian continual

reassessment methodology. In the phase 1 study in the US (8273-CL-0102), the MTD for ASP8273 has not yet been established, but estimated to be > 500 mg utilizing a similar Bayesian continual reassessment methodology. Based on the differential affinities for activating EGFR mutations relative to wild-type EGFR for ASP8273, dosing at the MTD is not necessarily required for antitumor activity, whereas the MTD is likely related to wild-type EGFR related toxicities. Of note, DLTs were observed in the 400 mg cohort of both phase 1 studies, and clinical antitumor responses were noted in dose levels of 100 mg and above in both studies.

Erlotinib and gefitinib are both approved for the treatment of NSCLC and the starting doses selected are consistent with current product labeling.

2.3 Endpoints

2.3.1 Primary Endpoints

- PFS as assessed by IRR

2.3.2 Secondary Endpoints

- OS
- Best overall response rate (CR + PR) by IRR
- PFS by the investigator
- Disease control rate (CR+PR+SD) by IRR
- DOR by IRR
- Safety variables (e.g., AEs, laboratory tests, vital sign measurements, ECGs)
- QoL and PRO parameters

2.3.3 Exploratory Endpoints

- Plasma T790M and other biomarkers related to EGFR TKI sensitivity and/or resistance
- Plasma pharmacokinetics of ASP8273
- PFS#2 on subsequent therapy

3 STUDY POPULATION

3.1 Selection of Study Population

First-line subjects with locally advanced, metastatic or unresectable stage IIIB/IV adenocarcinoma NSCLC (newly diagnosed or recurrent) with EGFR activating mutations (exon 19 deletion or exon 21 L858R) will be selected for this study. Subjects who have both an exon 19 deletion and exon 21 L858R mutation will not be included.

3.2 Inclusion Criteria

Subject must meet all of the following inclusion criteria to be eligible for participation in this study at enrollment:

1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written informed consent and privacy language as per national regulations (e.g., HIPAA Authorization for U.S. sites) must be obtained from the subject or legally authorized representative prior to any study-related procedures.
2. Subject is ≥ 18 years of age and legally an adult according to local regulation at the time of signing informed consent.
3. Subject agrees not to participate in another interventional study while on treatment.
4. Female subject must either:
    - Be of nonchildbearing potential:
        - postmenopausal (defined as at least 1 year without any menses) prior to Screening, or
        - documented surgically sterile
    - Or, if of childbearing potential:
        - Agree not to try to become pregnant during the study and for 28 days after the final study drug administration
        - And have a negative serum pregnancy test at Screening
        - And, if heterosexually active, agree to consistently use 2 forms of birth control* (at least 1 of which must be a highly effective method* and one must be a barrier method) starting at Screening and throughout the study period and for 28 days after the final study drug administration
5. Female subject must not be breastfeeding at Screening or during the study period, and for 28 days after the final study drug administration.
6. Female subject must not donate ova starting at Screening and throughout the study period, and for 28 days after the final study drug administration.
7. Male subject and their female spouse/partners who are of childbearing potential must be using highly effective contraception consisting of 2 forms of birth control* (1 of which must be a barrier method) starting at Screening and continue throughout the study period and for 90 days after the final study drug administration.

    *Highly effective forms of birth control include:
    - Consistent and correct usage of established oral, injected or implanted hormonal methods of contraception
    - Established intrauterine device (IUD) or intrauterine system (IUS)

    *Acceptable methods of birth control include:
    - Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository (not applicable in Japan and Thailand: with spermicidal foam/gel/film/cream/suppository)
    - Calendar-based contraceptive methods (Knaus-Ogino or rhythm method [Japan and Thailand only])

8. Male subject must not donate sperm starting at Screening and throughout the study period and for 90 days after the final study drug administration.
9. Subject has Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.
10. Subject has histologically confirmed locally advanced, metastatic or unresectable Stage IIIB/IV adenocarcinoma NSCLC (newly diagnosed or recurrent). Subjects with mixed histology are eligible if adenocarcinoma is the predominant histology.
11. Subject has predicted life expectancy ≥ 12 weeks in the opinion of the investigator.
12. Subject must meet all of the following criteria on the laboratory tests that will be analyzed centrally within 7 days prior to the first dose of study drug. In case of multiple laboratory data within this period, the most recent data should be used.
    - Neutrophil count > 1,000/mm^3
    - Platelet count ≥ 7.5 × 10^4 /mm^3
    - Hemoglobin > 8.0 g/dL
    - Serum creatinine < 2.0 x ULN or an estimated glomerular filtration rate (eGFR) of > 50 mL/min as calculated by the Cockcroft Gault Method
    - Total bilirubin < 1.5 × ULN (except for subjects with documented Gilbert's syndrome)
    - AST and ALT < 3.0 × ULN or ≤ 5 × ULN if subject has documented liver metastases
    - Serum sodium level is ≥ 130 mmol/L
13. Subject has an EGFR activating mutation (exon 19 deletion or exon 21 L858R), with or without T790M mutation, by local or central testing on examination of a NSCLC FFPE specimen (archival or fresh biopsy). Subjects harboring both exon 19 deletion and exon 21 L858R mutations are not eligible. A tissue sample from the same block used to determine eligibility by local testing should be available to send to the central lab for confirmatory testing. Subjects randomized based on local results indicating presence of EGFR mutation may remain on study if central results are discordant.
14. Subject must have at least 1 measureable lesion based on RECIST V1.1. Previously irradiated lesions will not be considered as measurable lesions.

Waivers to the inclusion criteria will **NOT** be allowed.

3.3 Exclusion Criteria

Subject who meets any of the following exclusion criteria prior to enrollment is not eligible for enrollment:

1. Subject has received intervening anticancer treatment or previous treatment with chemotherapy for metastatic disease other than palliative local radiation to painful bone metastases completed at least 1 week prior to the first dose of study drug. The administration of neoadjuvant or adjuvant chemotherapy is allowed as long as it has finalized ≥ 6 months before the first dose of study drug.

2. Subject has received a prior treatment with a therapeutic agent targeting EGFR (e.g., afatinib, dacomitinib, ASP8273, etc).
3. Subject has received investigational therapy within 28 days or 5 half-lives prior to the first dose of study drug.
4. Subject has received radiotherapy within 1 week prior to the first dose of study drug. If the subject received radiotherapy > 1 week prior to study treatment, the irradiated lesion cannot be the only lesion used for evaluating response.
5. Subject has symptomatic central nervous system (CNS) metastasis. Subject with previously treated brain or CNS metastases are eligible provided that the subject has recovered from any acute effects of radiotherapy, does not have brain metastasis related symptoms, is not requiring systemic steroids for at least 2 weeks prior to study drug administration, and any whole brain radiation therapy was completed at least 4 weeks prior to study drug administration or any stereotactic radiosurgery (SRS) was completed at least 2 weeks prior to study drug administration. Steroid inhaler use or ointment treatment for other concomitant medical disease is permitted.
6. Subject has received blood transfusions or hematopoietic factor therapy within 14 days prior to the first dose of study drug.
7. Subject has had a major surgical procedure (other than a biopsy) within 14 days prior to the first dose of study drug, or one is planned during the course of the study.
8. Subject has a known history of a positive test for human immunodeficiency virus (HIV) infection.
9. Subject has known history of serious hypersensitivity reaction to a known ingredient of ASP8273, erlotinib or gefitinib.
10. Subject has evidence of an active infection requiring systemic therapy within 14 days prior to the planned first dose of study drug.
11. Subject has severe or uncontrolled systemic diseases including uncontrolled hypertension (blood pressure > 150/100 mmHg) or active bleeding diatheses.
12. Subject has history of drug-induced ILD or any evidence of active ILD.
13. Subject has ongoing cardiac arrhythmia that is Grade ≥ 2 or uncontrolled atrial fibrillation of any grade.
14. Subject currently has Class 3 or 4 New York Heart Association congestive heart failure.
15. Subject has history of severe/unstable angina, myocardial infarction or cerebrovascular accident within 6 months prior to the planned first dose of study drug.
16. Subject has history of gastrointestinal ulcer or gastrointestinal bleeding within 3 months prior to the planned first dose of study drug.

17. Subject has concurrent corneal disorder or any ophthalmologic condition which, in the investigator's opinion, makes the subject unsuitable for study participation (i.e., advanced cataracts, glaucoma).
18. Subject has difficulty taking oral medication or any digestive tract dysfunction or inflammatory bowel disease that would interfere with the intestinal absorption of drug.
19. Subject has another past or active malignancy which requires treatment. Prior carcinoma in situ or non-melanoma skin cancer after curative resection are permitted.
20. Subject has any condition which, in the investigator's opinion, makes the subject unsuitable for study participation.
21. Subject has received potent CYP 3A4 inhibitors within 7 days prior to first dose of study drug or proton pump inhibitors such as omeprazole within 14 days prior to first dose of study drug.

Waivers to the exclusion criteria will **NOT** be allowed.

4 TREATMENT(S)

4.1 Identification of Investigational Product(s)

4.1.1 Test Drug(s)

ASP8273 will be provided as oral capsules in 100 mg strength packaged in HDPE bottles with child resistant cap and dessicant, containing 30 capsules each. ASP8273 should be stored at 20°C to 25°C (68-77°F) with excursions permitted to 15° to 30°C (59-86°F). Additional information regarding ASP8273 can be found in the ASP8273 Investigator's Brochure.

4.1.2 Comparative Drug(s)

Erlotinib will be provided as oral tablets in 150, 100 and 25 mg strengths in bottles containing 30 tablets each. Erlotinib should be stored at room temperature, 25°C (77°F) with excursions permitted to 15° to 30°C (59-86°F).

Gefitinib will be provided as oral tablets in 250 mg strength in blister packs containing 30 tablets each. Gefitinib should be stored at room temperature between 1°C and 30°C (33.8-86°F).

Comparative drugs will be provided by the study sponsor; however, should sponsor supplies become unavailable, site supplies may be used with prior approval from sponsor.

4.2 Packaging and Labeling

All medication provided by the sponsor in this study will be prepared, packaged, and labeled under the responsibility of qualified staff APGD-AUST or sponsor's designee in accordance with APGD-AUST or sponsor's designee standard operating procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, ICH GCP guidelines, and applicable local laws/regulations.

Each bottle will bear a label conforming to regulatory guidelines, GMP and local laws and regulations which identifies the contents as investigational drug.

4.3 Study Drug Handling

Current ICH GCP Guidelines require the investigator to ensure that study drug deliveries from the sponsor are received by the investigator/or designee and

- that such deliveries are recorded,
- that study drug is handled and stored according to labeled storage conditions,
- that study drug with appropriate expiry/retest and is only dispensed to study subjects in accordance with the protocol, and
- that any unused study drug is returned to the sponsor.

Drug inventory and accountability records for the study drugs will be kept by the investigator/ or designee. Study drug accountability throughout the study must be documented and reconciled. The following guidelines are therefore pertinent:

- The investigator agrees not to supply study drugs to any persons except the eligible subjects in this study in accordance with the protocol.
- The investigator or designee will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the investigator to dispense these test drugs.
- A study drug inventory will be maintained by the investigator or designee. The inventory will include details of material received and a clear record of when they were dispensed and to which subject.
- At the conclusion or termination of this study, the investigator or designee agrees to conduct a final drug supply inventory and to record the results of this inventory on the Drug Accountability Record. It must be possible to reconcile delivery records with those of used and/or returned medication. Any discrepancies must be accounted for and documented. Appropriate forms of deliveries and returns must be signed by the site staff delegated this responsibility.
- The site must return study drug to the sponsor or designee at the end of the study or upon expiration.

4.4 Blinding

This section is not applicable as this is an open-label study.

4.5 Assignment and Allocation

Randomization in a 1:1 ratio to each of the 2 treatment arms will be performed via Interactive Response Technology (IRT). Randomization will be stratified by ECOG PS (0, 1 or 2), EGFR mutation type (exon 19 deletion or mutation in exon 21 L858R), TKI chosen (erlotinib versus gefitinib) and race (Asian versus nonAsian). At the beginning of the trial, prior to site initiation and shipment of study drug supplies, each investigator will select either erlotinib or gefitinib to be utilized for all patients randomized to the comparator arm at their site. Prior to

the initiation of the study treatment, the site staff will contact the IRT in order to determine the randomly assigned treatment arm. Specific procedures for randomization through the IRT are contained in the study procedures manual.

5 TREATMENTS AND EVALUATION

5.1 Dosing and Administration of Study Drug(s) and Other Medication(s)

5.1.1 Dose/Dose Regimen and Administration Period

ASP8273 300 mg and erlotinib 150 mg will be taken orally once daily, on an empty stomach defined as no food for at least 2 hours before and 1 hour after dosing, at approximately the same time(s) every day.

Gefitinib 250 mg will be taken orally once daily, with or without food, at approximately the same time every day.

Concomitant medications should not be administered within 2 hours before or after dosing with ASP8273, erlotinib or gefitinib.

If a study drug dose is missed, it should be taken as soon as the subject remembers unless more than 12 hours has passed since the intended dosing time, in which case the subject should wait and take the next scheduled dose. Subjects should not make up a missed dose by taking a double dose at the next scheduled dose.

5.1.2 Increase or Reduction in Dose of the Study Drug(s)

Dosing for ASP8273, erlotinib or gefitinib may be interrupted for any event if the investigator deems it necessary to ensure subject safety. Dosing for ASP8273 or erlotinib may be reduced if necessary. Subjects requiring a treatment interruption should be re-evaluated not longer than 7 days from initial interruption and restarted on study drug as soon as clinically stable. The subject may be discontinued from treatment if there is an interruption of treatment for > 14 consecutive days despite optimal treatment of side effects. A discussion with the Medical Monitor should occur to confirm if the subject should continue on study treatment.

In the event of acute onset or worsening of pulmonary symptoms likely suggestive of ILD (dyspnea, cough, fever), study drug should be interrupted and a prompt investigation of these symptoms should occur and appropriate treatment initiated. If ILD is confirmed, study drug should be discontinued, and the subject should be treated appropriately per local standard of care.

Study drug should be interrupted if the subject experiences eye toxicity such as acute and severe eye pain or keratitis. Subjects with suspected keratitis should have study drug withheld until recovery and discontinued for persistent severe keratitis. Subjects with ocular toxicities should be evaluated by an ophthalmologist.

If the subject experiences severe hepatic impairment, study drug should be discontinued and the subject should be treated appropriately per local standard of care.

5.1.2.1 ASP8273 Dose Modification

Subjects requiring a dose reduction may be re-escalated one dose level (i.e., subjects reduced to 100 mg may only be re-escalated to 200 mg). If the event leading to the reduction recurs, the subject should be reduced to the lower dose level and not re-escalated again. If a grade 3 or 4 study drug-related toxicity persists, or recurs after 2 dose reductions, the subject will be permanently discontinued from ASP8273 treatment. Additionally, if after resolution of a Grade 4 event (except diarrhea, nausea and vomiting) requiring dose interruption and/or dose reduction, the event reoccurs at a G3 or higher the subject should be permanently discontinued from ASP8273.

Table 3 ASP8273 Dose Modification

Dose level	ASP8273 dose (mg qd)
Starting dose	300
-1	200
-2	100

Table 4 Events Requiring ASP8273 Dose Modification

ASP8273 Dose Modification Criteria	
Diarrhea, nausea, vomiting	
Grade 1	• Continue at same dose
Grade 2	• Continue at same dose if tolerable and manage as clinically indicated at the discretion of the investigator
Grade 3 or 4	• Interrupt dosing until the AE is managed to Grade ≤ 1 or baseline, then resume treatment at the same dose • If the AE recurs at Grade ≥ 3 when the same dose is resumed, then interrupt dosing until the AE is managed to Grade ≤ 1 or baseline, then resume treatment 1 dose level lower
Neuropathy	
Grade 1	• Continue at same dose
Grade 2	• Interrupt dosing at the discretion of the investigator until AE recovers to ≤ Grade 1 or baseline and resume treatment at the same dose. Investigate etiology of the neuropathy at the discretion of the investigator • If Grade 2 recurs after resuming study drug, reduce treatment to 1 dose level lower
Grade 3	• Interrupt dosing until the AE recovers to ≤ Grade 1 or baseline. Investigate etiology of the neuropathy at the discretion of the investigator • Dosing may be resumed, at the discretion of the investigator, 1 dose level lower • If Grade ≥ 3 recurs after resuming study drug, discontinue study drug permanently
Grade 4	• Permanently discontinue study drug and manage as clinically indicated at the discretion of the investigator

Table continued on next page

ASP8273 Dose Modification Criteria	
Hyponatremia	
Grade 1	• Recheck serum sodium levels as clinically indicated • In addition, urine osmolality, serum osmolality, and urine sodium concentrations should also be measured as clinically indicated • Dosing may continue without interruption at the discretion of the investigator
Grade 2	Not defined by NCI CTCAE v4.3
Grade 3	• For serum sodium levels < 130 – 125 mmol/L dosing may continue at the discretion of the investigator with additional monitoring as noted below • For serum sodium levels < 125 mm/L interrupt dosing • Serum sodium levels, serum osmolality, urine osmolality and urine sodium concentrations should be measured to determine the etiology of the hyponatremia and continue to be drawn as clinically indicated until the serum sodium levels recover ≤ Grade 1 or baseline • Consider fluid management plan if clinically indicated at the discretion of the investigator • Dosing should be held until serum sodium levels recover to ≤ Grade 1 or baseline, then dosing my resume, at the discretion of the investigator, at 1 dose level lower • If Grade ≥3 hyponatremia recurs after resuming ASP8273 at a reduced dose, ASP8273 may be discontinued
Grade 4	• Interrupt dosing immediately • Consider intravenous infusion of hypertonic saline, fluid management, or other management plan as clinically indicated at the discretion of the investigator • Serum sodium levels, serum osmolality, urine osmolality and urine sodium concentrations should be measured to determine the etiology of the hyponatremia and continue to be drawn as clinically indicated until the serum sodium levels recover ≤ Grade 1 or baseline • Correct sodium level at appropriate correction rate to avoid the risk of central pontine myelinolysis • Dosing should be held until serum sodium levels recover to ≤ Grade 1 or baseline, then treatment may resume, at the discretion of the investigator, at 1 dose level lower • If Grade ≥ 3 hyponatremia recurs after resuming drug at a reduced dose discontinue ASP8273

Table continued on next page

ASP8273 Dose Modification Criteria	
AST or ALT Elevation[1]	
Grade 3	• Interrupt dosing until the AE recovers to grade ≤ 1 or baseline, then resume treatment at the same dose level or 1 dose level lower at the discretion of the investigator • If Grade ≥ 3 AST or ALT elevation recurs after resuming study drug at the same dose level, an additional rechallenge at a reduced dose may be considered, at the discretion of the investigator, once the AE recovers to grade ≤ 1 or baseline. If Grade ≥ 3 AST or ALT elevation recurs after resuming study drug at a reduced dose, discontinue study drug
Grade 4	• Interrupt dosing until the AE recovers to grade ≤ 1 or baseline • At the discretion of the investigator, either discontinue study drug or resume study drug 1 dose level lower • If Grade ≥ 3 AST or ALT elevation recurs after resuming study drug at a reduced dose, discontinue study drug
Interstitial Lung Disease	
Any grade	• If ILD is suspected, ASP8273 should be interrupted immediately pending diagnostic evaluation. If ILD is diagnosed, ASP8273 should be discontinued permanently and appropriate treatment instituted as necessary.
Other adverse events, including ocular toxicity	
Grade 3	• Interrupt dosing until the AE recovers to grade ≤ 1 or baseline, then resume treatment at the same dose level or 1 dose level lower at the discretion of the investigator • If Grade ≥ 3 AE recurs after resuming study drug at the same dose, an additional rechallenge at a reduced dose may be considered, at the discretion of the investigator, once the AE recovers to grade ≤ 1 or baseline • If Grade ≥ 3 AE recurs after resuming study drug at a reduced dose, discontinue study drug
Grade 4	• Interrupt dosing until the AE recovers to grade ≤ 1 or baseline • At the discretion of the investigator, either discontinue study drug or resume study drug 1 dose level lower • If Grade ≥ 3 AE recurs after resuming study drug at a reduced dose, discontinue study drug

[1] Hold ASP8273 and repeat AST and ALT within 1 day to confirm abnormal results before discontinuing subject from ASP8273 treatment.

5.1.2.2 Erlotinib Dose Modification

Table 5 Erlotinib Dose Modification

Dose level	Erlotinib (mg qd)
Starting dose	150
-1	100
-2	50

Dose modifications for erlotinib are suggested for toxicities of ILD, skin rash, and diarrhea, however the locally approved label for erlotinib dose modification for toxicities should be followed. Subjects requiring dose reduction of erlotinib may have the dose re-escalated if they have been on a stable dose for ≥ 3 weeks without further toxicities requiring dose modification and it is considered by the investigator to be in the best interest of the subject. If any toxicity requiring dose interruption of erlotinib recurs despite the initial dose reduction to level -1 (100 mg qd), erlotinib may be reduced again to level -2 (50 mg qd). If 2 levels of erlotinib dose reduction are required, subsequent reescalation may only be to dose level -1.

Treatment with erlotinib should be used with extra caution in subjects with total bilirubin > 3 x ULN. Erlotinib dosing should be interrupted or discontinued if changes in liver function are severe such as doubling of total bilirubin and/or tripling of transaminases in the setting of pretreatment values outside normal range. In the setting of worsening liver function tests, before they become severe, dose interruption and/or dose reduction with frequent liver function test monitoring should be considered. Erlotinib dosing should be interrupted or discontinued if total bilirubin is > 3 x ULN and/or transaminases are > 5 x ULN in the setting of normal pretreatment value.

Table 6 Events Requiring Erlotinib Dose Modification

Erlotinib Dose Modification Criteria	
Toxicity (NCI CTCAE v4.03)	**Dose Modification[1] for Erlotinib**
Diarrhea	
Grade 1 or 2	None. Initiate therapy with antidiarrhea medication as needed
Grade 3[2] or 4[2]	Interrupt erlotinib until resolution to ≤ grade 2 and then restart 1 dose level lower
Rash	
Grade 1	None
Grade 2	None. If rash persists and is intolerable or worsens over 10-14 days, then reduce by 1 dose level and initiate treatment as outlined in protocol.
Grade 3[2]	Reduce by 1 dose level. If rash persists or worsens over 10-14 days, then interrupt erlotinib until resolution to ≤ grade 2 and then restart 1 dose level lower.
Grade 4	Permanently discontinue erlotinib
Interstitial Lung Disease	
Any Grade	If ILD is suspected, erlotinib should be interrupted immediately pending diagnostic evaluation. If ILD is diagnosed, erlotinib should be discontinued permanently and appropriate treatment instituted as necessary.
Other Toxicities, including ocular toxicity	
Grade 1 or 2	None
Grade 3 [2, 3]	Interrupt erlotinib until resolution to ≤ grade 2 and then restart 1 dose level lower
Grade 4	Permanently discontinue erlotinib

Footnotes appear on next page

[1] Doses that have been reduced to 100 mg/day may be reescalated to 150 mg/day, but only if the toxicity that led to the dose reduction has abated or returned to baseline severity, and the investigator believes it is in the best interest of the subject. Doses that have been reduced to 50 mg/day may be reescalated to 100 mg/day, but only if the toxicity that led to the dose reduction has abated or returned to baseline severity, and the investigator believes it is in the best interest of the subject. **Doses that have been reduced to 50 mg/day may never be re-escalated to a dose higher than 100 mg/day**. Any subject who fails to tolerate treatment with 50 mg/day will be discontinued from erlotinib and enter the posttreatment period of the study.

[2] If the event does not resolve to ≤ grade 2 by ≤ 14 days, erlotinib will be discontinued.

[3] Only if ≥ 2 grade level change from baseline

5.1.2.3 Gefitinib Dose Modification

There will be no dose reductions for subjects receiving gefitinib as it is only available as a single strength tablet. Below summarizes recommended therapy interruption for gefitinib; however, the locally approved label should be followed for additional guidance.

Gefitinib Dose Modification Criteria	
Toxicity (NCI CTCAE v4.03)	**Dose Modification for Gefitinib**
Diarrhea	
Persistent Grade 2 or ≥ Grade 3	Interrupt gefitinib up to 14 days. Resume treatment when event resolves to Grade ≤ 1or baseline.
Skin Reactions	
≥ Grade 3	Interrupt gefitinib up to 14 days. Resume treatment when event resolves to Grade ≤ 1or baseline.
Interstitial Lung Disease	
Any Grade	In the event of acute onset or worsening of pulmonary symptoms suggestive of ILD (dyspnea, cough fever), gefitinib should be interrupted immediately pending diagnostic evaluation. If ILD is confirmed, gefitinib should be discontinued permanently and appropriate treatment instituted as necessary.
AST, ALT or bilirubin elevation	
≥ Grade 2	Interrupt gefitinib up to 14 days. Resume treatment when event resolves to Grade ≤ 1or baseline.
Other Toxicities, including ocular toxicity	
≥ Grade 3	Interrupt gefitinib up to 14 days. Resume treatment when event resolves to Grade ≤ 1or baseline.

If ILD, persistent severe keratitis, severe hepatic impairment or gastrointestinal perforation is confirmed, gefitinib should be discontinued, and the subject should be treated appropriately per local standard of care.

5.1.3 Previous and Concomitant Treatment (Medication and Nonmedication Therapy)

All medications and concomitant treatments administered from 28 days prior to cycle 1 day 1 must be recorded in the eCRF. Documentation will include the medication name, indication, route and dates of administration.

Arm A (ASP8273)

The following medications/food are likely to influence evaluation of the safety, pharmacokinetics or efficacy of ASP8273 and will be strictly prohibited:

	Prohibited Medications/Food	Reason to Exclude
1	Chemotherapy, radiotherapy, immunotherapy, or other medications intended for antitumor activity	Likely affect efficacy, safety or pharmacokinetics of ASP8273
2	Investigational products or therapy other than ASP8273	
3	Potent inhibitors (e.g., ketoconazole, grapefruit or grapefruit juice) or inducers (e.g., rifampin, phenytoin or St. John's wort) of CYP3A4	ASP8273 is a substrate of CYP3A4
4	CYP3A4 and/or P-gp substrates with a narrow therapeutic index[1]	ASP8273 may be an inhibitor of CYP3A4 and/or P-gp

[1] The drugs defined as CYP Substrates with Narrow Therapeutic Range by FDA's guidance - Guidance for Industry Drug Interaction Studies - Study Design, Data analysis, and Implications for Dosing and Labeling): http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf)

The use of the following medications should be avoided or used with caution and closely monitored.

	Medications to be Avoided or Used with Caution	Reason to be Cautious
1	Moderate/weak inhibitors or inducers of CYP3A4	ASP8273 is a substrate of CYP3A4
2	Inhibitors or inducers of P-gp	ASP8273 is a substrate of P-gp
3	CYP3A4 and/or P-gp substrates	ASP8273 may be an inhibitor of CYP3A4 and/or P-gp

Arm B (Erlotinib/Gefitinib)

The following medications/food are likely to influence evaluation of the safety, pharmacokinetics or efficacy of erlotinib/gefitinib, and will be strictly prohibited:

Prohibited Medications/Food		Reason to Exclude
All Subjects	Chemotherapy, radiotherapy, immunotherapy, or other medications intended for antitumor activity other than erlotinib/gefitinib	Likely affect efficacy, safety or pharmacokinetics of erlotinib or gefitinib
	Investigational products or therapy	
	Potent inhibitors (e.g., ketoconazole, grapefruit or grapefruit juice) or inducers (e.g., rifampin, phenytoin or St. John's wort) of CYP3A4	Erlotinib and gefitinib are substrates of CYP3A4
	Proton pump inhibitors or drugs that cause significant elevation in gastric pH	Elevation in gastric pH may reduce bioavailability of erlotinib or gefitinib

The use of the following medications should be avoided or used with caution and closely monitored:

Medications to be Avoided or Used with Caution		Reason to be Cautious
All Subjects	Moderate/weak inhibitors or inducers of CYP3A4	Erlotinib and gefitinib are substrates of CYP3A4
	Inhibitors or inducers of P-gp	Erlotinib and gefitinib are substrates of P-gp
	Warfarin	INR elevations and/or bleeding events have been noted in subjects taking warfarin while on erlotinib and gefitinib therapy
Subjects receiving erlotinib	Potent inhibitors of CYP1A2	Erlotinib is a substrate of CYP1A2
Subjects receiving gefitinib	Potent inhibitors of CYP2D6	Gefitinib is a substrate of CYP2D6
	CYP2D6 substrates with narrow therapeutic index[1]	Gefitinib is an inhibitor of CYP2D6

1 The drugs defined as CYP Substrates with Narrow Therapeutic Range by FDA's guidance - Guidance for Industry Drug Interaction Studies - Study Design, Data analysis and Implications for Dosing and Labeling): (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf)

5.1.4 Treatment Compliance

The dose of ASP8273 or erlotinib/gefitinib administered to each subject will be recorded on the subject diary and entered in to the eCRF. Reasons for dose interruption, reduction or omission will also be recorded. This information, plus study drug accountability at every cycle will be used to assess compliance with the treatment.

Any subject who misses > 14 consecutive days of study drug dosing, on either treatment arm, may be discontinued from the study upon discussion between the investigator and sponsor's Medical Monitor.

5.2 Demographics and Baseline Characteristics

5.2.1 Demographics

Demographic information will be collected for all subjects and will include initials (where allowed), date of birth, sex, race, ethnicity and tobacco use history (pack years).

5.2.2 Medical History

Medical history includes all significant medical conditions other than NSCLC that have resolved prior to informed consent or are ongoing at the time of consent. Details that will be collected include the onset date and recovery date and CTCAE grade, if applicable for ongoing conditions.

5.2.3 Diagnosis of the Target Disease, Severity, and Duration of Disease

A complete medical history of the target disease will be recorded at Screening. This will include:

- NSCLC diagnosis (date and method of diagnosis, including dates of diagnostic procedures)
- TNM classification and disease stage at screening
- EGFR mutation status and method used to determine status (e.g., sequencing or PCR-based assay)
- Dates and type of previous therapy or surgery for NSCLC
- Other disease-specific information as designated in the eCRF

5.2.4 Performance Status

The ECOG Scale [Oken, 1982] will be used to assess performance status. Refer to [Appendix 12.10].

5.3 Efficacy Assessment

Response and progression will be evaluated in this study using RECIST V1.1 (see [Appendix 12.9]).

Imaging will be performed and assessed at Screening (baseline) and every 56 days (± 7 days) throughout the study. Imaging of the brain is required at baseline for all subjects, and may be repeated throughout the study as clinically indicated. If a brain lesion not previously irradiated is selected as a target lesion at baseline, the assessment should be repeated at all subsequent imaging timepoints. Scans should be scheduled in such a way to allow for the results to be available for the day 1 visit of each odd cycle (cycle 3, 5, 7 etc). Baseline imaging performed prior to informed consent as standard of care may be used so long as it is performed within 28 days prior to randomization and will meet the comparability requirements outlined below.

Scans will be read on site and also submitted in digital format for blinded independent central review until PFS#1 has been confirmed for each subject.

CT scan with contrast (chest and abdomen) is the preferred modality for tumor assessment. MRI is acceptable if local standard practice, or CT scans are contraindicated in a subject (e.g., subject is allergic to contrast media). All other RECIST-approved scanning methods such as x-ray are optional. PET-CT scans must use contrast. Additional instructions for imaging assessments can be found in the study procedures manual.

The assessment will include tumor measurements for target lesions, non-target lesions and any new lesions.An overall assessment will be characterized for a given time point evaluation. At the end of study for that subject, the best overall response to the study regimen will be characterized. To ensure comparability, the screening and subsequent assessment of response should be performed using identical techniques. The same individual should assess images for any 1 subject for the duration of the study if possible. For subjects with known brain metastases at study entry, it is recommended that repeat imaging also include the brain

and the same methods used to detect brain lesions at baseline are to be used to follow the lesions throughout the study.

Confirmation scans for CR or PR should be done at the next scheduled assessment. If a subject discontinues study drug prior to disease progression, the subject should continue to undergo local imaging assessment every 56 days (± 7 days) until PD is documented per investigator, the subject misses 2 or more consecutive scheduled tumor assessments, or the subject starts another anticancer treatment, whichever occurs earlier, in order to assess PFS#1.

The site of disease progression including target, non-target and/or new lesions should be documented in the eCRF. Additional imaging may be performed at any time to confirm suspected progression of disease.

5.3.1 Evaluation of Target Lesions

5.3.1.1 Complete Response (CR)

CR is defined as disappearance of all target and nontarget lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm from baseline measurement.

5.3.1.2 Partial Response (PR)

PR is defined as at least a 30% decrease in the sum of diameters (longest for nonnodal lesions, short axis for nodal lesions) of target lesions taking as reference to the baseline sum of diameters.

5.3.1.3 Stable Disease (SD)

SD is defined as neither sufficient decrease to qualify for PR nor sufficient increase to qualify for progressive disease taking as reference the smallest sum of diameters while on study drug.

5.3.1.4 Progressive Disease (PD)

PD is defined as at least a 20% increase in the sum of diameters (longest for nonnodal lesions, short axis for nodal lesions) of the 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 5 mm. The appearance of 1 or more new lesions is also considered progression.

5.3.2 Evaluation of Nontarget Lesions

To achieve unequivocal progression on the basis of nontarget lesions, there must be an overall level of substantial worsening in nontarget disease such that, even in presence of SD or PR of target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of 1 or more nontarget lesions is usually not sufficient to qualify for unequivocal progression.

5.3.2.1 Complete Response (CR)

For CR of nontarget lesions, subjects must have disappearance of all nontarget lesions and all lymph nodes must be nonpathological in size (< 10 mm short axis).

5.3.2.2 NonCR/NonPD

NonCR/NonPD of nontarget lesions is defined as persistence of 1 or more nontarget lesions.

5.3.2.3 Progressive Disease (PD)

PD of nontarget lesions is defined as unequivocal progression of existing nontarget lesions or the appearance of 1 or more new lesions.

5.3.3 Evaluation of Time Point Response

The overall response status at each time point for subjects with measurable disease at baseline will be reported according to Table 1 in [Appendix 12.9].

5.3.4 Disease Control Rate (DCR)

The disease control rate is defined as the proportion of subjects whose best overall response is rated as CR, PR or SD among all analyzed subjects.

5.3.5 Progression-free Survival (PFS)

PFS is defined as the time from randomization to death from any cause or radiographic disease progression assessed according to RECIST V1.1, whichever occurs first.

5.4 Safety Assessment

5.4.1 Vital Signs

Vital signs, including systolic and diastolic blood pressures (mmHg), radial pulse rate (beats/minute) and temperature will be obtained according to the Schedule of Assessments and recorded. All vital sign measures will be obtained with the subject in the sitting or supine position.

If clinically significant vital sign changes from baseline (pretreatment) are noted, the changes will be documented as AEs on the AE page of the eCRF. Clinical significance will be defined as a variation in vital signs, which has medical relevance as deemed by the investigator that could result in an alteration in medical care. The investigator will continue to monitor the subject until the parameter returns to Grade ≤ 1, or to the baseline (pretreatment) value, or until the investigator determines that follow up is no longer medically necessary.

5.4.2 Adverse Events

Adverse event collection will begin from time of informed consent and continue through the 30-day follow-up visit, regardless of initiation of a new anticancer therapy or transfer to hospice. Serious adverse events considered related to the study drug should continue to be reported as long as the subject is being followed after study drug discontinuation and has not started a new anticancer treatment. Adverse events will be documented at each clinic visit,

but can be collected at any time. Any AE that meets the definition of an SAE will also be reported on a separate form to the sponsor.

See [Section 5.5] for information regarding AE collection and data handling.

5.4.2.1 Adverse Events of Possible Hepatic Origin

See [Appendix 12.2] for detailed information on liver abnormalities, monitoring and assessment, if the AE for a subject enrolled in a study and receiving study drug is accompanied by increases in liver function testing (LFT, e.g., AST, ALT, total bilirubin, etc.) or is suspected to be due to hepatic dysfunction.

Subjects with AEs of hepatic origin accompanied by Liver Function Test (LFT) abnormalities should be carefully monitored.

5.4.3 Laboratory Assessments

A table of the laboratory tests that will be performed during the conduct of the study is found in [Appendix 12.11]. Laboratory tests will be performed predose according to the Schedule of Assessments and sent to a central laboratory for analysis. Additional assessments may be done centrally or locally to monitor adverse events or as required by dose modification requirements.

Additional laboratory tests should be performed according to institutional standard of care. Clinical significance of out-of-range laboratory findings is to be determined and documented by the investigator or delegated Subinvestigator who is a qualified physician.

5.4.4 Physical Examination

Standard, full physical examinations will be performed to assess general appearance, skin, eyes, ears, nose, throat, neck, cardiovascular, chest and lungs, abdomen, musculoskeletal, neurologic status, mental status, and lymphatic systems. Physical examinations will be conducted at visits as outlined in the Schedule of Assessments. Each physical examination will include the observation and review of all body systems, and weight; height is only required at Screening. If clinically significant worsening of findings from baseline is noted at any study visit, the changes will be documented as AEs on the AE eCRF. Clinical significance is defined as any variation in physical findings, which has medical relevance that could result in an alteration in medical care. The investigator will continue to monitor the subject until the parameter returns to Grade ≤ 1, or to the baseline condition, or until the investigator determines that follow-up is no longer medically necessary.

5.4.5 Electrocardiogram (ECG)

Single 12-lead ECGs will be conducted at visits as outlined in the Schedule of Assessments and assessed locally. Whenever another study procedure time point coincides with an ECG time point, study procedures should be performed in the following sequence: ECG first, followed by vital signs, followed by any type of blood collection (safety labs or pharmacokinetics) last.

5.5 Adverse Events and Other Safety Aspects

5.5.1 Definition of Adverse Events (AEs)

An AE is defined as any untoward medical occurrence in a subject administered a study drug or has undergone study procedures and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Some countries may have additional local requirements for events that are required to be reported as AEs or in an expedited manner similar to an SAE. In these cases, it is the investigator's responsibility to ensure these AEs or other reporting requirements are followed and the information is appropriately recorded in the eCRF accordingly.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, ECG data, physical exam) should be defined as an AE only if the abnormality meets 1 of the following criteria:

- Induces clinical signs or symptoms
- Requires active intervention
- Requires interruption or discontinuation of study medication
- The abnormality or investigational value is clinically significant in the opinion of the investigator.

The development of a new cancer should be regarded as an AE and will generally meet at least 1 of the serious criteria. New cancers are those that are not the primary reason for the administration of the study drug and have been identified after the subject's inclusion in this study. It does not include new metastases of the original cancer.

5.5.2 Definition of Serious Adverse Events (SAEs)

An AE is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Results in death
- Is life threatening (an AE is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death)
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly, or birth defect
- Requires inpatient hospitalization or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious)
- Other medically important events

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent 1 of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Disease progression can be considered as the worsening of a subject's condition attributable to NSCLC. 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 metastases to the primary cancer under study should be considered as disease progression and not an AE. Events which are unequivocally due to disease progression should not be reported as an AE during the study.

Progression of NSCLC, including signs and symptoms of progression, should not be reported as an SAE unless it results in death within 30 days of the last dose of study drug. For progression-related death reported as an SAE as required, there should be available immediate cause of death reported as the event term. "Death due to disease progression" should be recorded as the adverse event term only when the cause of death cannot be otherwise determined.

Safety events of interest on the medicinal products administered to the subject as part of the study (e.g., study drug, comparator, background therapy) that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of the medicinal product(s)
- Suspected abuse/misuse of the medicinal product(s)
- Inadvertent or accidental exposure to the medicinal product(s)
- Medication error involving the medicinal product(s) (with or without subject/patient exposure to the sponsor medicinal product (e.g., name confusion)

All of the events of interest noted above should be recorded on the eCRF. Any situation involving these events of interest that also meets the criteria for an SAE should be recorded on the AE page of the eCRF and marked 'serious' and the SAE worksheet.

The sponsor has a list of events that they classify as "always serious" events. If an AE is reported that is considered to be an event per this classification as "always serious", additional information on the event may be requested.

5.5.3 Criteria for Causal Relationship to the Study Drug

Adverse events that fall under either "Possible" or "Probable" should be defined as "AEs whose relationship to the study drugs could not be ruled out".

Causal relationship to the study drug	Criteria for causal relationship
Not Related	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and/or in which other drugs, chemicals or underlying disease provide plausible explanations.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals and which follows a clinically reasonable response on re administration (rechallenge) or withdrawal (de-challenge).

5.5.4 Criteria for Defining the Severity of an Adverse Event

AEs, including abnormal clinical laboratory values, will be graded using the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Event (CTCAE) guidelines (Version 4.03). The items that are not stipulated in the NCI-CTCAE Version 4.03 will be assessed according to the criteria below and entered into the eCRF:

Grade	Assessment Standard
1-Mild	Asymptomatic, or mild symptoms, clinical or diagnostic observations noted; intervention not indicated.
2-Moderate	Local or noninvasive intervention indicated.
3-Severe	Medically significant but not immediately life threatening, hospitalization or prolonged hospitalization.
4-Life Threatening	Life threatening consequences, urgent intervention indicated
5-Death	Death related to AE

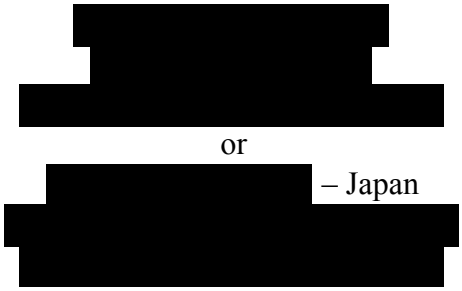
5.5.5 Reporting of Serious Adverse Events (SAEs)

In the case of an SAE, the investigator must contact the sponsor/delegated CRO by telephone or fax immediately (within 24 hours of awareness).

The investigator should complete and submit an SAE Worksheet containing all information that is required by the Regulatory Authorities to the sponsor/delegated CRO by fax or email immediately (within 24 hours of awareness). If the faxing of an SAE Worksheet is not possible or is not possible within 24 hours, the local drug safety contact should be informed by phone.

If there are any questions, or if clarification is needed regarding the SAE, please contact the sponsor's Medical Monitor/Expert or his/her designee (see Section II).

Please fax or email the SAE worksheet for Japan (JUTOKUNA YUUGAIJISHOU HOUKOKUSHO) to:

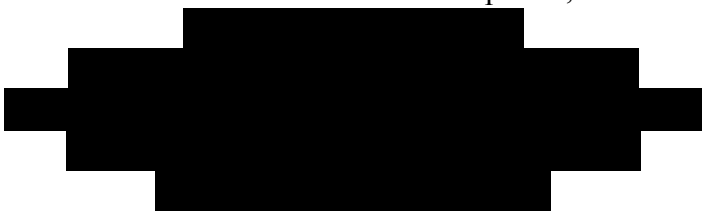


or

– Japan

Please fax or email the SAE worksheet for ROW to:

Astellas Pharma Global Development, Inc.



Follow-up information for the event should be sent promptly (within 7 days of the initial notification.

Full details of the SAE should be recorded on the medical records and on the eCRF.

The following minimum information is required:

- ISN/Study number,
- Subject number, sex and age,
- The date of report,
- A description of the SAE (event, seriousness of the event), and
- Causal relationship to the study drug.

The sponsor or sponsor's designee will submit expedited safety reports (i.e., IND Safety Reports) to the regulatory agencies (i.e., FDA) as necessary, and will inform the investigators of such regulatory reports. Investigators must submit safety reports as required by their IRB/IEC within timelines set by regional regulations (i.e., EU, eCTD, FDA). Documentation of the submission to and receipt by the IRB/IEC of expedited safety reports should be retained by the site.

The sponsor/delegated CRO will notify all investigators responsible for ongoing clinical studies with the study drug of all SAEs which require submission per local requirements of the IRB/IEC.

The investigators should provide written documentation of IRB/IEC notification for each report to the sponsor.

You may contact the sponsor's Medical Monitor/Expert for any other problem related to the safety, welfare or rights of the subject.

5.5.6 Follow-up of Adverse Events

All AEs occurring during or after the subject has discontinued the study are to be followed up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized.

If during AE follow-up, the AE progresses to an ″SAE″, or if a subject experiences a new SAE, the investigator must immediately report the information to the sponsor.

Please refer to [Appendix 12.2] for detailed instructions on drug-induced liver injury (DILI).

5.5.7 Monitoring of Common Serious Adverse Events

Common SAEs are SAEs commonly anticipated to occur in the study population independent of drug exposure. SAEs classified as “common” are provided in [Appendix 12.3]. The list does NOT change reporting obligations or prevent the need to report an AE meeting the definition of an SAE as detailed above. The purpose of this list is to provide an alert that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of “common SAEs” as specified in [Appendix 12.3]. The sponsor will monitor these events throughout the course of the study for any change in frequency. Any changes to this list will be communicated to the participating investigational sites. Investigators must report individual occurrences of these events as stated in [Section 5.5.5].

5.5.8 Procedure in Case of Pregnancy

If a female subject or partner of a male subject becomes pregnant during the study dosing period or within 90 days from the discontinuation of dosing, the investigator should report the information to the sponsor/delegated CRO as if it is an SAE. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result and neonatal data etc., should be included in this information.

The investigator will follow the medical status of the mother, as well as the fetus, as if the pregnancy is an SAE and will report the outcome to the sponsor.

When the outcome of the pregnancy falls under the criteria for SAEs (spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly [including anomaly in a miscarried fetus]), the investigator should respond in accordance with the reporting procedure for SAEs. Additional information regarding the outcome of a pregnancy (which is categorized as an SAE) is mentioned below.

- "Spontaneous abortion" includes miscarriage, abortion and missed abortion
- Death of an infant within 1 month after birth should be reported as an SAE regardless of its relationship with the study drug
- If an infant dies more than 1 month after the birth, it should be reported if a relationship between the death and intrauterine exposure to the study drug is judged as "possible" by the investigator
- In the case of a delivery of a living newborn, the "normality" of the infant is evaluated at the birth

- Unless a congenital anomaly are identified prior to spontaneous abortion or miscarriage, the embryo or fetus should be assessed for congenital defects by visual examination

If during the conduct of a clinical trial, a male subject makes his partner pregnant, the subject should report the pregnancy to the investigator. The investigator will report the pregnancy to the sponsor/delegated CRO as an SAE.

5.5.9 Emergency Procedures and Management of Overdose

In the event of suspected ASP8273 overdose, the subject should receive supportive care and monitoring. The Medical Monitor should be contacted as applicable.

In the event of suspected erlotinib or gefitinib overdose, refer to the approved Package Insert, SPC or local product information supplied by the manufacturer for each agent.

5.5.10 Supply of New Information Affecting the Conduct of the Study

When new information becomes available necessary for conducting the clinical study properly, the sponsor will inform all investigators involved in the clinical study as well as the regulatory authorities. Investigators should inform the IRB/IEC of such information when needed.

The following 2 paragraphs are applicable to investigational sites in Japan:

1. When information is obtained regarding serious and unexpected adverse drug reactions (or other) that are specified in Article 273 of the Enforcement Regulations of the Pharmaceutical Affairs Law, in compliance with Article 80-2 Paragraph 6 of the Pharmaceutical Affairs Law, the sponsor should inform all the investigators involved in the clinical study, the head of the study site, and the regulatory authorities of such information. The head of the study site who receives such information will decide whether the clinical study should be continued after hearing the opinions of the IRB. The investigator will supply the new information to the subjects, in compliance with [Section 8.2.3.2].
2. In addition to the above item (1), when the head of the study site receives the revisions of the Investigator's Brochure, protocol, or written information, information on the matters covering the quality of the study drug, efficacy and safety, information necessary for conducting the clinical study properly, or documents to be examined by the IRB should be sent to the IRB.

5.5.11 Deviations from the Protocol and Other Actions Taken to Avoid Life-threatening Risks to Subjects (Unique to Japan)

The investigator must not deviate from or amend the protocol, excluding an emergency case for avoiding risks to the subjects. When the investigator does not follow the protocol in order to avoid urgent risks for subjects, the investigator should take the following actions.

1. Describe the contents of the deviation or amendment and the reasons for it in a written notice, and immediately send the document stating the deviation or amendment and the reasons to the sponsor and the head of the study site. Keep a copy of the notice.

2. Consult with the sponsor at the earliest possibility for cases in which it is necessary to amend the protocol. Obtain approval for a draft of the amended protocol from the IRB and the head of the study site as well as written approval from the sponsor.

5.6 Test Drug Concentration

5.6.1 Pharmacokinetics

Blood samples will be collected to analyze plasma concentrations of unchanged ASP8273 and its metabolite(s) (if applicable) in subjects randomized to the ASP8273 arm as outlined in the Schedule of Assessments. For each ASP8273 sample, 2 mL of blood will be collected in a draw tube designated for research use only and processed. Blood sampling, processing, storage and shipment instructions will be provided in the Lab Manual. Samples will be shipped to and analyzed by a sponsor-designated analytical laboratory. Please refer to the Lab Manual for more detailed information.

5.7 Other Measurements, Assessments or Methods

5.7.1 Quality of Life and Patient Reported Outcomes

Subjects will be asked to complete the QoL and PRO questionnaires electronically at baseline and at day 1 of each cycle where a visit takes place. The questionnaires should be administered prior to the start of any assessments and before the disease status is discussed with the patient. The EQ-5D-5L only will also be administered at each of the posttreatment or long-term follow-up survival contacts for 6 months after treatment discontinuation.

5.7.1.1 FACT-EGFRI-18

The FACT-EGFR-18 is a PRO instrument specifically designed to assess the effect of EGFR inhibitors on quality of life. It consists of 18 items in 3 QoL domains: symptoms, functioning and emotions.

5.7.1.2 EORTC-QLQ-LC13

The EORTC-QLQ-LC13 module items evaluate lung cancer-specific symptoms such as cough, hemoptysis, shortness of breath, sore mouth or tongue, dysphagia, tingling hands or feet, hair loss and pain.

5.7.1.3 EORTC-QLQ-C30

The EORTC-QLQ-C30 is a 30-item cancer-specific instrument consisting of 5 functional domain scales: physical, role, emotional, social and cognitive.

5.7.1.4 EQ-5D-5L

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome, consisting of 6 items that cover 5 main domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a general visual analog scale for health status.

5.7.2 Biomarkers

Plasma and whole blood samples will be collected as specified in the schedule of assessments for exploratory analysis of biomarkers and EGFR mutation status. Formalin fixed paraffin embedded (FFPE) specimen, either from an archival specimen or from a recent biopsy, will be collected from all subjects. Eligibility may be determined by a previously documented EGFR mutation test result (L858R or exon 19 del). However, there should be sufficient tumor tissue from the specimen used to generate the EGFR test result to send to the central lab for confirmatory testing (10 unstained slides or FFPE block preferred, 7 slides minimum). If slides are submitted, the slides should be freshly cut from the FFPE block within 18 days of sending to the central lab. If a subject does not have a previously documented EGFR mutation test result, then a fresh formalin fixed paraffin embedded specimen (surgical resection, core needle biopsy or fine needle aspiration) must be obtained and set to the central lab for eligibility testing. Tissue slides may be retained for analysis at the central laboratory for up to 15 years.

A plasma sample for EGFR mutation detection will also be collected at baseline and at end of treatment and submitted to the central laboratory. For subjects who signed a separate ICF, an optional post-progression tumor tissue for exploratory analysis of biomarkers (e.g., EGFR mutation [T790M, C797S], c-Met mutation/amplification and AXL over expression) which are potentially related to EGFR-TKI drug response or resistance, will be collected following locally or centrally confirmed disease progression and prior to commencement of subsequent anticancer therapy.

Plasma and tissue sampling, processing, storage and shipment instructions will be provided in the lab manual. Samples will be shipped to and analyzed by a sponsor-designated analytical laboratory. Please refer to the Lab Manual for more detailed instructions.

5.7.3 Sample for PGx Substudy

PGx research may be conducted in the future to analyze or determine genes of relevance to clinical response, pharmacokinetics and toxicity/safety issues. After randomization (see Schedule of Assessments), a 4-mL sample of whole blood for possible retrospective PGx analysis will be collected and processed. Blood sampling, processing, storage and shipment instructions will be provided in the Lab Manual. Samples will be shipped to and analyzed by a sponsor-designated analytical laboratory. Please refer to the Lab Manual for more detailed information.

See [Appendix 12.4] for further details on the banking procedures.

5.8 Total Amount of Blood

The total amount of blood collected for study assessments for each subject will vary depending on how long they stay on treatment.

At any time during the study, if any laboratory abnormalities are found for a subject or for disease assessment, additional blood may be drawn for monitoring.

Additional blood beyond standard monitoring that will be drawn for this study will include draws for eligibility assessment, hematology, chemistry, and coagulation at specific study defined time points, pharmacokinetics and bioanalytical sampling.

The maximum amount of blood collected per cycle is approximately 28.2 mL in cycle 1.

6 DISCONTINUATION

6.1 Discontinuation of Individual Subject(s)

A discontinuation is a subject who enrolled in the study and for whom study treatment is permanently discontinued for any reason.

The subject is free to withdraw from the study treatment and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

The subject will be discontinued from the treatment period if any of the following occur:

- Subject develops radiological progressive disease (i.e., PFS#1) per RECIST v1.1 based on central confirmation of investigator assessment
    - If there is radiographic evidence of PD by investigator, however the investigator believes the subject is continuing to derive clinical benefit (asymptomatic and/or without worsening of performance status or overall health) from study drug, and an increase in tumor burden is not likely to affect vital organ function, the subject may remain on study drug until the next scheduled radiographic assessment which should occur after 56 days (± 7 days).
    - If the next radiographic assessment indicates PD per RECIST 1.1 which is confirmed by the central reviewer, then the subject must be discontinued from study drug.
    - In the rare event where PD suspected on initial assessment is not confirmed on subsequent scan by the investigator or central reviewer, the subject may continue in the study.
    - The investigator should make every effort to immediately submit radiographic assessments for central review when PD is either suspected or confirmed or uncertainty exists.
    - In case of PD determination by the investigator, however not confirmed by the central reviewer, and subject is progressing clinically and requires new anti-cancer treatment immediately, the subject should be discontinued.
- Subject is required to receive local or systemic anti-cancer treatment based on investigator’s clinical opinion.
- Subject develops unacceptable toxicity
- Female subject becomes pregnant

- Investigator decides it is in the subject's best interest to discontinue including clinical progression
- Requirement for significant surgical procedure; however, if surgical procedure is for the resection of the primary or metastatic lesion, the subject may be eligible to continue on study treatment after discussion with the Medical Monitor
- Significant deviation from the protocol or eligibility criteria
- Subject declines further treatment
- Subject is noncompliant with the protocol based on the investigator or Medical Monitor assessment
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject
- Death

The subject may be discontinued from the study if there is an interruption of treatment for > 14 consecutive days despite optimal treatment of side effects. A discussion with the Medical Monitor should occur to confirm if the subject should continue on study treatment.

Subjects who discontinue study drug and enter the posttreatment follow up period prior to reaching PFS#1 will be discontinued from the posttreatment period if any of the following occur:

- Subject develops radiological progressive disease (i.e., PFS#1) based on investigator assessment
- Subject initiates a new systemic anticancer treatment
- Subject misses 2 consecutive scheduled tumor assessments

The subject will be discontinued from the long-term follow-up period (for PFS#2) if any of the following occur:

- Subject initiates a new systemic anticancer treatment (3^{rd} line)
- Subject exhibits evidence of PD from 2^{nd} line therapy based on investigator assessment
- Subject declines further study participation (i.e., withdraws consent)
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject
- Death
- Sponsor ends long-term follow-up collection period

The subject will be discontinued from the survival follow-up period if any of the following occur:

- Subject declines further study participation (i.e., withdraws consent)
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject
- Death
- Sponsor ends survival follow-up period

6.2 Discontinuation of the Site

If an investigator intends to discontinue participation in the study, the investigator must immediately inform the sponsor.

6.3 Discontinuation of the Study

The sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. Advance notice is not required if the study is stopped due to safety concerns. If the sponsor terminates the study for safety reasons, the sponsor will immediately notify the investigator and subsequently provide written instructions for study termination.

7 STATISTICAL METHODOLOGY

The statistical analysis will be coordinated by the responsible biostatistician of APGD. A Statistical Analysis Plan (SAP) will be written to provide details of the analysis, along with specifications for tables, listings and figures to be produced. The SAP will be finalized before enrollment of the first subject. Any changes from the analyses planned in SAP will be justified in the clinical study report (CSR).

Prior to Database Lock, a Final Review of Data and TLFs Meeting will be held to allow a review of the clinical trial data and to verify the data that will be used for analysis set classification. If required, consequences for the statistical analysis will be discussed and documented. A meeting to determine analysis set classifications may also be held prior to database lock.

In general, all data will be summarized with descriptive statistics (number of subjects, mean, standard deviation, minimum, median and maximum) for continuous endpoints, and frequency and percentage for categorical endpoints.

7.1 Sample Size

Approximately 600 subjects will be randomized in a 1:1 ratio to 2 treatment arms: Arm A (ASP8273) and Arm B (erlotinib or gefitinib). Randomization will be stratified by ECOG PS (0, 1 or 2), EGFR mutation type (exon 19 deletion or mutation in exon 21 [L858R]), TKI chosen (erlotinib versus gefitinib) and race (Asian versus nonAsian). Assuming HR=0.667 (median PFS in Arm A and Arm B are 15.6 months and 10.4 months, respectively), a total of 420 PFS events will provide approximately 98.7% power to detect a statistically significant difference at type I error rate of 1-sided 0.025.

7.2 Analysis Set

Detailed criteria for analysis sets will be laid out in Classification Specifications and the allocation of subjects to analysis sets will be determined prior to database hard-lock.

7.2.1 Full Analysis Set (FAS)

The full analysis set will consist of all subjects who are randomized. This will be the primary analysis set for efficacy analyses.

7.2.2 Per Protocol Set (PPS)

The per protocol set will consist of the subset of the FAS who do not meet criteria for PPS exclusion. These criteria are to capture relevant nonadherence to the protocol and will be defined in the SAP. In addition, subjects in the PPS are required to have both baseline imaging and at least 1 postbaseline imaging scan. The PPS will be a secondary analysis set for efficacy analyses. Select demographic and baseline characteristics may also be summarized for the PPS.

7.2.3 Safety Analysis Set (SAF)

For the statistical summary of the safety data, the safety analysis set (SAF) will be used. The SAF consists of all subjects who take at least 1 dose of study medication, and will be used for safety analyses.

7.2.4 Pharmacokinetic Analysis Set (PKAS)

The pharmacokinetic analysis set (PKAS) consists of the subset of the SAF population for which at least one plasma concentration data is available for whom the time of dosing on the previous day of sampling is known. Additional subjects may be excluded from the PKAS at the discretion of the pharmacokineticist. Any formal definitions for exclusion of subjects or time-points from the PKAS will be documented in the Classification Specifications and determined in the Classification Meeting.

7.2.5 Pharmacodynamics Analysis Set (PDAS)

The biomarker pharmacodynamics analysis set (PDAS) will include the subjects from the SAF population for whom sufficient pharmacodynamic measurements were collected. The PDAS will be used for all analyses of pharmacodynamics data.

7.3 Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized by treatment group for the SAF. Descriptive statistics will include number of subjects, mean, standard deviation, minimum, median and maximum for continuous endpoints, and frequency and percentage for categorical endpoints.

7.4 Analysis of Efficacy

Efficacy analysis will be conducted on the FAS and PPS. The interpretation of results from statistical tests will be based on the FAS. The PPS will be used to assess the robustness of the results from the statistical tests based on the FAS. All randomized subjects will be analyzed according to the treatment to which they are randomized.

7.4.1 Analysis of Primary Endpoint

7.4.1.1 Primary Analysis

The primary endpoint is PFS assessed by the blinded IRR. For each subject, PFS is defined as the time from the date of randomization until the date of radiological disease progression (i.e., PFS#1) assessed by IRR, or until death due to any cause. If a subject has neither progressed nor died, the subject will be censored at the date of last radiological assessment. Subjects who receive any further anticancer therapy for the disease before radiological progression will be censored at the date of the last radiological assessment before the anticancer therapy started. If progression or death occurs after missing 2 scheduled radiological assessments, the subject will be censored at the date of last radiological assessment or at the date of randomization if no postbaseline radiological assessment is available.

The primary analysis will be performed when approximately 420 PFS#1 events have been observed.

The distribution of PFS will be estimated for each treatment arm using Kaplan-Meier methodology and compared between Arm A and Arm B using log-rank test stratified by ECOG PS (0 and 1 combined versus 2), EGFR mutation type, and TKI chosen (erlotinib versus gefitinib). In addition, stratified Cox proportional hazard model will be used to estimate the hazard ratio and the corresponding 95% confidence interval.

The primary analysis will be performed using the FAS.

7.4.1.2 Secondary Analysis

The same analysis of the primary endpoint as described in [Section 7.4.1.1] will be conducted using the PPS.

7.4.1.3 Subgroup Analysis

The analysis described in [Section 7.4.1.1] will be conducted in the subgroups using the FAS.

Forest plot will be presented to illustrate the strength of treatment effects across subgroups defined by baseline factors.

7.4.2 Analysis of Secondary Endpoints

7.4.2.1 Overall survival

OS is defined as the time from the date of randomization until the documented date of death from any cause. All events of death will be included, regardless of whether the event occurred while the subject is still taking study drug or after the subject discontinue study drug. Subjects who are still alive at the time of analysis will be censored at the last day known to be alive.

The distribution of OS will be estimated for each treatment arm using Kaplan-Meier methodology and compared between Arm A and Arm B using the log-rank test stratified by ECOG PS (0 and 1 combined versus 2), EGFR mutation type (exon 19 deletion or mutations in exon 21 [L858R]) and TKI chosen (erlotinib versus gefitinib). In addition, stratified Cox

proportional hazard model will be used to estimate the hazard ratio and the corresponding 95% confidence interval.

7.4.2.2 Best overall response rate (ORR)

Best overall response is determined once all tumor response data for the subject is available. Subjects will be classified by best response on study as outlined in RECIST V1.1 criteria. For best overall response of SD, SD must be documented as present at least once after study entry and at least 7 weeks after first dose.

The ORR is defined as the proportion of subjects with a complete or partial objective response based on the RECIST V1.1.

The ORR (confirmed) is defined as the proportion of subjects with a confirmed complete or partial objective response based on the RECIST V1.1 in Table 3 of [Appendix 12.9].

The comparison of ORR between Arm A and Arm B will be performed using stratified CMH test. In addition, ORR for each arm will be estimated and corresponding 95% confidence interval will be constructed.

The comparison of ORR (confirmed) between Arm A and Arm B will be performed using stratified CMH test. In addition, ORR for each arm will be estimated and corresponding 95% confidence interval will be constructed. This will be a sensitivity analysis.

Hochberg procedure will be used to control the overall error rate at 1-sided 0.025 level for the secondary efficacy endpoints (OS and ORR). Only when the primary endpoint significantly favors the ASP8273 arm will secondary endpoints be tested.

7.4.2.3 PFS by the Investigator

For each subject, PFS is defined as the time from the date of randomization until the date of radiological disease progression assessed by the investigator, or until death due to any cause. If a subject has neither progressed nor died, the subject will be censored at the date of last radiological assessment. Subjects who receive any further anticancer therapy for the disease before radiological progression will be censored at the date of the last radiological assessment before the anticancer therapy started. If progression or death occurs after missing 2 consecutive scheduled radiological assessments, the subject will be censored at the date of last radiological assessment or at the date of randomization if no postbaseline radiological assessment is available.

The distribution of PFS will be estimated for each treatment arm using Kaplan-Meier methodology and compared between Arm A and Arm B using stratified log-rank test as specified in [Section 7.4.1.1]. In addition, stratified Cox proportional hazard model will be used to estimate the hazard ratio and the corresponding 95% confidence interval.

7.4.2.4 Disease Control Rate (DCR)

The DCR is defined as the proportion of subjects with a complete or partial objective response or a stable disease based on RECIST V1.1.

The comparison of DCR between Arm A and Arm B will be performed using CMH test stratified by ECOG PS (0 and 1 combined versus 2), EGFR mutation type (exon 19 deletion or mutations in exon 21 [L858R]) and TKI chosen (erlotinib versus gefitinib). In addition, DCR for each arm will be estimated and corresponding 95% confidence interval will be constructed.

7.4.2.5 Duration of Response (DOR)

DOR is defined as the time from the date of the first response CR/PR (whichever is first recorded) as assessed by IRR to the date of radiographic progression or date of censoring. If a subject has not progressed, the subject will be censored at the date of last radiological assessment or at the date of first CR/PR if no post-baseline radiological assessment is available.

The distribution of DOR will be estimated for each treatment arm using Kaplan-Meier methodology and compared between Arm A and Arm B using the log-rank test stratified by ECOG PS (0 and 1 combined versus 2), EGFR mutation type (exon 19 deletion or mutations in exon 21 [L858R]) and TKI chosen (erlotinib versus gefitinib). In addition, stratified Cox proportional hazard model will be used to estimate the hazard ratio and the corresponding 95% confidence interval.

7.4.2.6 QoL and PRO Parameters

Descriptive QoL and PRO analyses will be performed on the FAS. Completion rate for each questionnaire will be summarized. Additional analyses will be discussed in details in the statistical analysis plan.

7.4.3 Analysis of Exploratory Endpoints

7.4.3.1 PFS on Next-Line Therapy (PFS#2)

PFS#2 is defined as the time from initiation of new systemic anti-cancer treatment (excluding local radiation, surgical removal of metastatic site or protocol defined Erlotinib or Geftinib or ASP8273 based on initial treatment allocation per subject) to investigator-determined progression, discontinuation of new treatment, start of a different treatment or death from any cause, whichever comes first. Otherwise, subjects will be censored.

Subjects who have not started new systemic anti-cancer treatment will be censored at Day 1. Subjects who are alive, started new systemic anti-cancer treatment and for whom a PFS#2 event has not been observed should be censored at the last time known to be alive.

The distribution of PFS#2 will be estimated for each treatment arm using Kaplan-Meier methodology and compared between Arm A and Arm B using stratified log-rank test as specified in [Section 7.4.1.1]. In addition, stratified Cox proportional hazard model will be used to estimate the hazard ratio and the corresponding 95% confidence interval.

7.4.3.2 Other Exploratory Analyses

Exploratory assessment of pharmacokinetic-pharmacodynamic relationships will be performed.

7.5 Analysis of Safety

All treated subjects will be analyzed according to the treatment they received.

7.5.1 Adverse Events

Adverse events will be coded using MedDRA. The number and percentage of AEs, SAEs, AEs leading to discontinuation and AEs related to study drug will be summarized by system organ class, preferred term and treatment group. The number and percentage of AEs by severity will also be summarized. All AEs will be listed.

7.5.2 Laboratory Assessments

For quantitative laboratory measurements descriptive statistics will be used to summarize results and change from baseline by treatment group and time point. Shifts relative to normal ranges from baseline to each time point during treatment period in lab tests will also be tabulated. Laboratory data will be displayed in listings.

7.5.3 Vital Signs

Descriptive statistics will be used to summarize vital sign results and changes from baseline by treatment group and time. Vital signs data will be displayed in listings.

7.5.4 Physical Examination

Physical examination will be listed by treatment group.

7.5.5 ECGs

The 12-lead ECG results will be summarized by treatment group and time point.

7.5.6 Concomitant Medication

The frequency of concomitant medications (prescription, over-the-counter, and nutritional supplements) will be summarized by preferred term. Medications will be coded using the WHO drug dictionary. Medications will be counted by the number of subjects who took each medication. To count the number of subjects who took a medication, a subject taking the same medication multiple times will only be counted once for that medication. Medications will be presented in decreasing order of frequency based on the total number of subjects who took each medication.

7.5.7 ECOG Performance Status

Summary statistics (number and percent of subjects) for each category of the ECOG performance status at each assessment will be provided. The change from baseline to final visit or early termination will also be summarized. Negative change scores indicate an improvement. Positive scores indicate a decline in performance.

7.6 Analysis of Pharmacokinetics

Descriptive statistics (e.g., N, mean, standard deviation, minimum, median, maximum, coefficient of variation and geometric mean) will be provided for plasma concentrations of

ASP8273 and its metabolite(s) (if applicable) at each visit. Additional model-based analyses may be performed and reported separately.

7.7 Analysis of Biomarkers

Exploratory analysis may be performed for plasma biomarkers. Details will be provided in the SAP.

7.8 Protocol Deviations and Other Analyses

Protocol deviations as defined in [Section 8.1.6] will be summarized for all subjects in the FAS by treatment group and site totals will also be provided. A data listing will be provided by site and subject.

The protocol deviation criteria will be uniquely identified in the summary table and listing. The unique identifiers will be as follows:

PD1 - Entered into the study even though they did not satisfy entry criteria,

PD2 - Developed withdrawal criteria during the study and was not withdrawn,

PD3 - Received wrong treatment or incorrect dose,

PD4 - Received excluded concomitant treatment.

7.9 Interim Analysis (and Early Discontinuation of the Clinical Study)

An interim futility analysis is planned to occur after 210 PFS events are observed, which is expected to occur approximately 22 months after the first subject is randomized. If the observed HR is less than 1.1, recruitment into the study will continue as planned until 600 subjects are recruited. If the observed HR at the interim is larger than 1.1, recruitment into the study may be stopped at the interim analysis. Further review of the efficacy data, including secondary endpoints, will be performed by the sponsor to determine whether other evidence of clinical benefit justifies reopening enrollment. If the data do not justify reopening enrollment, enrollment may remain closed, and a decision will be made by the sponsor regarding termination of the study. If the futility analysis takes place after enrollment is completed and the HR is greater than 1.1, subjects who in the opinion of the investigator and the sponsor's Medical Monitor are continuing to derive benefit may continue to receive study drug as randomized. As the interim analysis is for futility only, type I error at final analysis will not be affected.

The interim analysis will be conducted by the IDMC. In addition safety data reviews during the trial will be conducted by the IDMC on a periodic basis. For example, the IDMC will review safety data after the first 50 patients have been randomized and on study drug for approximately 3 months. The full procedures for IDMC safety review will be described in a separate IDMC charter.

7.10 Handling of Missing Data, Outliers, Visit Windows, and Other Information

As a general principle, no imputation of missing data will be done. Exceptions are the start and stop dates of AEs and concomitant medication. The imputed dates will be used to allocate the concomitant medication and AEs to a treatment group, in addition to determining whether an AE is/is not treatment-emergent. Listings of the AEs and concomitant medications will present the actual partial dates; imputed dates will not be shown.

Subjects with missing overall response assessment will be regarded as nonresponders in ORR analysis.

8 OPERATIONAL AND ADMINISTRATIVE CONSIDERATIONS

8.1 Procedure for Clinical Study Quality Control

8.1.1 Data Collection

The investigator or site designee will enter data collected using an Electronic Data Capture (EDC) system. In the interest of collecting data in the most efficient manner, the investigator or site designee should record data (including laboratory values, if applicable) in the eCRF within 5 days after the subject visit.

The investigator or site designee is responsible to ensure that all data in the eCRFs and queries are accurate and complete and that all entries are verifiable with source documents. These documents should be appropriately maintained by the site.

The monitor should verify the data in the eCRFs with source documents and confirm that there are no inconsistencies between them.

Laboratory tests are performed at a central laboratory. Laboratory data will be transferred electronically to the sponsor or designee at predefined intervals during the study. The laboratory will provide the sponsor or designee with a complete and clean copy of the data.

For Screen failures the demographic data, reason for failing, informed consent, inclusion and exclusion criteria and AEs will be collected in the eCRF.

<u>ePRO</u>

Subject diaries and questionnaires will be completed by the subject or site (as applicable for phone collection of QoL) on an electronic device. The information completed by the subject on the electronic device will be automatically uploaded into a central website. The investigator or site designee should review the diaries and questionnaire data on the website for correct completion while the subject is at the site. The diary and questionnaire data will be transferred electronically to the sponsor or designee at predefined intervals during the study. The vendor will provide sponsor or designee with a complete and clean copy of the data.

8.1.2 Specification of Source Documents

Source data must be available at the site to document the existence of the study subjects and to substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the subject.

The following information should be included in the source medical records:

- Demographic data (date of birth, sex, race, ethnicity, height and body weight)
- Inclusion and exclusion criteria details
- Participation in study and original signed and dated ICFs
- Visit dates
- Medical history and physical examination details
- Key efficacy and safety data, if applicable (as specified in the protocol)
- Adverse events and concomitant medication
- Results of relevant examinations (e.g., ECG charts, X-ray films etc.)
- Smoking history (in pack-years)
- Laboratory printouts
- Dispensing and return of study drug details
- Reason for premature discontinuation (if applicable)
- Randomization number

8.1.3 Clinical Study Monitoring

The sponsor or delegated CRO is responsible for monitoring the clinical study to ensure that subject's human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol and GCP, and study data reported by the investigator/subinvestigator are accurate and complete and that they are verifiable with study-related records such as source documents. The sponsor is responsible for assigning study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

8.1.4 Direct Access to Source Data/Documents

The investigator and the study site must accept monitoring and auditing by the sponsor or delegated CRO as well as inspections from the IRB/IEC and relevant regulatory authorities. In these instances, they must provide all study-related records, such as source documents (refer to [Section 8.1.2]) when they are requested by the sponsor monitors and auditors, the IRB/IEC, or regulatory authorities. The confidentiality of the subject's identities shall be well protected consistent with local and national regulations when the source documents are subject to direct access.

8.1.5 Data Management

Data Management will be coordinated by Data Science of the sponsor in accordance with the SOPs for data management. All study-specific processes and definitions will be documented by Data Management. eCRF completion will be described in the eCRF instructions. Coding

of medical terms and medications will be performed using MedDRA and WHO Drug Dictionary respectively.

8.1.6 Protocol Deviations

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety and welfare of subjects. The investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to trial subjects.

A protocol waiver is a documented prospective approval of a request from an investigator to deviate from the protocol. Protocol waivers are strictly prohibited.

For the purposes of this protocol, deviations requiring notification to the sponsor are defined as any subject who:

- Entered into the study even though they did not satisfy entry criteria
- Developed withdrawal criteria during the study and not withdrawn
- Received wrong treatment or incorrect dose
- Received excluded concomitant treatment

When a deviation from the protocol is identified for an individual subject, the investigator or designee must ensure the sponsor is notified. The sponsor will follow-up with the investigator, as applicable, to assess the deviation and the possible impact to the safety and/or efficacy of the subject to determine subject continuation in the study.

If a deviation impacts the safety of a subject, the investigator must contact the sponsor immediately.

The investigator will also assure that deviations meeting IRB/IEC and applicable regulatory authorities' criteria are documented and communicated appropriately. All documentation and communications to the IRB/IEC and applicable regulatory authorities will be provided to the sponsor and maintained within the Trial Master File (TMF).

NOTE: Other deviations outside of the categories defined above that are required to be reported by the IRB/IEC in accordance with local requirements will be reported, as applicable.

8.1.7 End of Trial in All Participating Countries

The study completion is defined as the conclusion of data collection for the defined study endpoints. Subjects continuing to derive clinical benefit are allowed to continue to receive treatment in the study after study completion. The end of study in all participating countries is therefore defined as the Last Subject's Last Visit, or last contact. The study may be closed within a participating country per local regulations after the study has completed if all subjects enrolled in the country are no longer receiving study treatment.

8.2 Ethics and Protection of Subject Confidentiality

8.2.1 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)/Competent Authorities (CA)

GCP requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) as well as any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, ICF and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any substantial amendments to the protocol will require IEC/IRB approval prior to implementation of the changes made to the study design at the site. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

Any SAEs that meet reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to the sponsor.

If required by local regulations, the investigator shall make accurate and adequate written progress reports to the IEC/IRB at appropriate intervals, not exceeding 1 year. The investigator shall make an accurate and adequate final report to the IRB/IEC within 90 days after the close-out visit for APGD-sponsored studies, or for APEB/APEL-sponsored studies within 1 year after last subject out (LSO) or termination of the study.

8.2.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki.

8.2.3 Informed Consent of Subjects

8.2.3.1 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject or his/her guardian or legal representative, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the ICF will be reviewed and signed and dated by the subject or his/her guardian or legal representative, the person who administered the informed consent and any other signatories according to local requirements. A copy of the signed ICF will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated

source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

The signed consent forms will be retained by the investigator and made available (for review only) to the study monitor and auditor regulatory authorities and other applicable individuals upon request.

8.2.3.2 Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information

1. The investigator or his/her representative will immediately inform the subject orally whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue to participate in the study (e.g., report of serious drug adverse drug reaction). The communication must be documented in the subject's medical records and must document whether the subject is willing to remain in the study or not.
2. The investigator must update their ICF and submit it for approval to the IRB/IEC. The investigator or his/her representative must obtain written informed consent from the subject on all updated ICFs throughout their participation in the study. The investigator or his/her designee must reconsent subjects with the updated ICF even if relevant information was provided orally. The investigator or his/her representative who obtained the written informed consent and the subject should sign and date the ICF. A copy of the signed ICF will be given to the subject and the original will be placed in the subject's medical record. An entry must be made in the subject's records documenting the reconsent process.

8.2.4 Subject Confidentiality

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Such medical information may be given only after approval of the subject to the subject's physician or to other appropriate medical personnel responsible for the subject's well-being.

The sponsor shall not disclose any confidential information on subjects obtained during the performance of their duties in the clinical study without justifiable reasons.

The sponsor affirms the subject's right to protection against invasion of privacy. Only a subject identification number and/or initials will identify subject data retrieved by the sponsor. However, the sponsor requires the investigator to permit the sponsor, sponsor's representative(s), the IRB/IEC and when necessary, representatives of the regulatory health authorities to review and/or to copy any medical records relevant to the study.

The sponsor will ensure that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal and/or regional legislation related to the privacy and protection of personal information (i.e., HIPAA).

8.3 Administrative Matters

8.3.1 Arrangement for Use of Information and Publication of the Clinical Study

Information concerning the study drug, patent applications, processes, unpublished scientific data, the Investigator's Brochure and other pertinent information is confidential and remains the property of the sponsor. Details should be disclosed only to the persons involved in the approval or conduct of the study. The investigator may use this information for the purpose of the study only. It is understood by the investigator that the sponsor will use the information obtained during the clinical study in connection with the development of the drug and therefore may disclose it as required to other clinical investigators or to regulatory agencies. In order to allow for the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide the sponsor with all data obtained during the study.

Publication of the study results is discussed in the Clinical Study Agreement.

8.3.2 Documents and Records Related to the Clinical Study

The investigator will archive all study data (e.g., Subject Identification Code List, source data, eCRFs and Investigator's File) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation (for US sites, 2 years after approval of the NDA or discontinuation of the IND). The sponsor will notify the site/investigator if the NDA/MAA/J-NDA is approved or if the IND/IMPD/CHIKEN TODOKE is discontinued. The investigator agrees to obtain the sponsor's agreement prior to disposal, moving, or transferring of any study-related records. The sponsor will archive and retain all documents pertaining to the study according to local regulations.

Data generated by the methods described in the protocol will be recorded in the subjects' medical records and/or study progress notes. All data will be entered in the eCRFs for each subject.

8.3.3 Protocol Amendment and/or Revision

Any changes to the study that arise after approval of the protocol must be documented as protocol amendments: substantial amendments and/or nonsubstantial amendments. Depending on the nature of the amendment, either IRB/IEC, Competent Authority approval or notification may be required. The changes will become effective only after the approval of the sponsor, the investigator, the regulatory authority and the IRB/IEC (if applicable).

Amendments to this protocol must be signed by the sponsor and the investigator. Written verification of IRB/IEC approval will be obtained before any amendment is implemented which affects subject safety or the evaluation of safety, and/or efficacy. Modifications to the protocol that are administrative in nature do not require IRB/IEC approval, but will be submitted to the IRB/IEC for their information, if required by local regulations.

If there are changes to the Informed Consent, written verification of IRB/IEC approval must be forwarded to the sponsor. An approved copy of the new Informed Consent must also be forwarded to the sponsor.

8.3.4 Insurance of Subjects and Others

The sponsor has covered this study by means of an insurance of the study according to national requirements. The name and address of the relevant insurance company, the certificate of insurance, the policy number and the sum insured are provided in the Investigator's File.

If a subject suffers any study-related injury, the sponsor will compensate appropriately according to the severity and duration of the damage. However, if it was caused intentionally or was due to gross negligence by the study site, the sponsor will consult with the study site about handling the injury, based on the agreed study contract. Compensation for the study-related injury is provided by the following procedures:

1. If a subject incurs an injury as a result of participation in the clinical study, the study site should provide medical treatment and other necessary measures. The sponsor should be notified of the injury.
2. When the subject claims compensation from the study site for the above study-related injury, or such compensation may be claimed, the study site should immediately communicate the fact to the sponsor. Both parties should work together towards compensation settlement.
3. The sponsor shall pay compensation or indemnification and bear expenses necessary for the settlement as provided in the clinical contract.
4. The sponsor shall make an arranging for insurance and take measures necessary to ensure the compensation or indemnification mentioned above.

8.3.5 Signatory Investigator for Clinical Study Report

ICH E3 guidelines recommend and EU Directive 2001/83/EC requires that a final study report which forms part of a marketing authorization application be signed by the representative for the Coordinating Investigator(s) or the Principal Investigator(s). The representative for the Coordinating Investigator (s) or the Principal Investigator(s) will have the responsibility to review the final study results to confirm to the best of his/her knowledge it accurately describes the conduct and results of the study. The representative for Coordinating Investigator(s) or the Principal Investigator(s) will be selected from the participating investigators by the sponsor prior to database lock.

9 QUALITY ASSURANCE

The sponsor is implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented, recorded and reported in compliance with the protocol, GCP and applicable regulatory requirement(s).

The sponsor or sponsor's designee may arrange to audit the clinical study at any or all investigational sites and facilities. The audit may include on-site review of regulatory

documents, case report forms, and source documents. Direct access to these documents will be required by the auditors.

10 STUDY ORGANIZATION

10.1 Independent Data-Monitoring Committee (IDMC) | Data and Safety Monitoring Board (DSMB) | Monitoring Committee | Other Evaluation Committee(s)

An independent Data Monitoring Committee will be responsible for evaluating safety data on a periodic basis during the study and to review results of the planned futility analysis. The IDMC will minimally consist of medically qualified individuals and a statistician. A separate IDMC charter will specify the governance and conduct of the IDMC.

10.2 Other Study Organization

Not applicable.

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Package Insert, Erlotinib, Genentech/Astellas, 2012 (available at https://www.astellas.us/docs/tarceva.pdf)

Package Insert, Gefitinib, Astrazeneca, 2014 (available at http://www.iressa.com/product-information.html)

Data on file for ASP8273

12 APPENDICES

12.1 List of Excluded Concomitant Medications

The following medications/food are likely to influence evaluation of the safety, pharmacokinetics or efficacy of ASP8273 or erlotinib/gefitinib, and will be strictly prohibited:

Arm A (ASP8273)	**Arm B (Erlotinib/Gefitinib)**
• Chemotherapy, radiotherapy, immunotherapy or other medications intended for antitumor activity. • Investigational products or therapy other than ASP8273. • Potent inhibitors or inducers of CYP3A4 • CYP3A4 and/or P-gp substrates with a narrow therapeutic index	• Chemotherapy, radiotherapy, immunotherapy or other medications intended for antitumor activity other than erlotinib/gefitinib. • Investigational products or therapy. • Potent inhibitors or inducers of CYP3A4 • Proton pump inhibitors or drugs that cause significant elevation in gastric pH

Examples for excluded inhibitors, inducers and substrates for enzymes and transporters are provided below. This list should NOT be considered all inclusive. Investigators will consult individual drug labels to determine liability of the drugs.

Excluded CYP Inhibitors/Inducers		
CYP3A4	**Inhibitors**	**Potent**: boceprevir, clarithromycin, conivaptan, grapefruit juice*, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole *The effect of grapefruit juice varies widely among brands and is concentration-, dose- and preparation dependent.
	Inducers	**Potent**: avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort

Excluded Drugs with Narrow Therapeutic Index	
CYP3A4 substrates	Alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine
P-gp substrates	Cyclosporine, digoxin, sirolimus

Additional information for inhibitors/inducers/substrates of enzymes/transporters can be found in FDA's guidance (Guidance for Industry Drug Interaction Studies - Study Design, Data analysis, and Implications for Dosing and Labeling)[1] and from the Division of Clinical Pharmacology of Indiana University[2].

1. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf
2. http://medicine.iupui.edu/clinpharm/ddis/main-table/

12.2 Liver Safety Monitoring and Assessment

Any subject enrolled in a clinical study with active drug therapy and reveals an increase of serum aminotransferases (AT) to > 3 × ULN (to > 5 × ULN in subjects with liver metastases), or total bilirubin > 2 × ULN, should undergo detailed testing for liver enzymes (including at least ALT, AST, ALP, and TBL). Testing should be repeated within 48 to 72 hours of notification of the test results. Alerts will be generated by the central lab regarding moderate and severe liver abnormality to inform the investigator, study monitor and study team. Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

Confirmed abnormalities will be characterized as moderate and severe where ULN:

	ALT or AST		**Total Bilirubin**
Moderate	> 3 x ULN (in patients without liver metastases), > 5 x ULN (in patients with liver metastases)	or	> 2 x ULN
Severe*	> 3 x ULN	and	> 2 x ULN

In addition, the subject should be considered to have severe hepatic abnormalities for any of the following:

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks (in the absence of liver metastases)
- ALT or AST > 3 × ULN and INR > 1.5 (If INR testing is applicable/evaluated).
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

The investigator may determine that abnormal liver function results, other than as described above, may qualify as moderate or severe abnormalities and require additional monitoring and follow-up.

Follow-up Procedures

Confirmed moderate and severe abnormalities in hepatic functions should be thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination and laboratory tests. The site should complete the Liver Abnormality Case Report Form (LA-CRF) that has been developed globally and can be activated for any study. Subjects with confirmed abnormal liver function testing should be followed as described below.

Confirmed moderately abnormal LFTs should be repeated 2 to 3 times weekly then weekly or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic.

Severe hepatic liver function abnormalities as defined above, in the absence of another etiology may be considered an important medical event and may be reported as an SAE. The

sponsor should be contacted and informed of all subjects for whom severe hepatic liver function abnormalities possibly attributable to study drug are observed.

To further assess abnormal hepatic laboratory findings, the investigator is expected to:

- Obtain a more detailed history of symptoms and prior or concurrent diseases. Symptoms and new onset-diseases should be recorded as 'AEs' on the AE page of eCRF. Illnesses and conditions such as hypotensive events, and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Nonalcoholic steatohepatitis (NASH) is seen in obese hyperlipoproteinemic, and/or diabetic patients and may be associated with fluctuating aminotransferase levels. The investigator should ensure that the medical history form captures any illness that predates study enrollment that may be relevant in assessing hepatic function.
- Obtain a history of concomitant drug use (including nonprescription medication, complementary and alternative medications), alcohol use, recreational drug use and special diets. Medications, including dose, should be entered on the concomitant medication page of the eCRF. Information on alcohol, other substance use and diet should be entered on the LA-CRF or an appropriate document.
- Obtain a history of exposure to environmental chemical agents.
- Based on the subject's history, other testing may be appropriate including:
  - acute viral hepatitis (A, B, C, D, E or other infectious agents).
  - ultrasound or other imaging to assess biliary tract disease
  - other laboratory tests including INR, direct bilirubin
- Consider gastroenterology or hepatology consultations.
- Submit results for any additional testing and possible etiology on the LA-CRF or an appropriate document.

Study Discontinuation

In the absence of an explanation for increased LFT's, such as viral hepatitis, preexisting or acute liver disease, presence of liver metastases, or exposure to other agents associated with liver injury, the subject may be discontinued from the study. The investigator may determine that it is not in the subject's best interest to continue study enrollment. Discontinuation of treatment should be considered if:

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks (in subjects without liver metastases
- ALT or AST > 3 × ULN and TBL > 2 × ULN or INR > 1.5 (If INR testing is applicable/evaluated)
- ALT or AST > 5 × ULN and (TBL > 2 × ULN in patients with liver metastases)
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

In addition, if close monitoring for a subject with moderate or severe hepatic laboratory tests is not possible, drug should be discontinued.

*Hy's Law Definition-Drug-induced jaundice caused by hepatocellular injury, without a significant obstructive component, has a high rate of bad outcomes, from 10% to 50% mortality (or transplant)." The 2 "requirements" for Hy's Law are: 1) evidence that a drug can cause hepatocellular-type injury, generally shown by an increase in transaminase elevations higher than 3 times the upper limit of normal ("2 x ULN elevations are too common in treated and untreated patients to be discriminating") and 2) cases of increased bilirubin (at least 2 x ULN) with concurrent transaminase elevations at least 3 x ULN and no evidence of intra- or extra-hepatic bilirubin obstruction (elevated alkaline phosphatase) or Gilbert's syndrome [Temple 2006].

References

Guidance for Industry titled "Drug-Induced Liver Injury: Premarketing Clinical Evaluation" issued by FDA on July 2009.

Temple R. Hy's law: predicting serious hepatotoxicity. Pharmacoepidemiol Drug Saf. 2006 Apr;15(4):241-3.

12.3 Common Serious Adverse Events

The following is a list of SAEs that the sponsor considers to be associated with the disease state being studied. **The list does NOT change reporting obligations or prevent the need to report an AE meeting the definition of an SAE as detailed in** [**Section 5.5.2**]. The purpose of this list is to provide an alert that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of "common SAEs". You are required to follow the requirements detailed in [Section 5.5.5].

For IND safety reporting, single occurrences of the following events may be excluded from expedited reporting to the FDA. If aggregate analysis of these events indicates they occur more frequently with study drug, an expedited IND safety report may be submitted to the FDA.

AEs most likely related to NSCLC (Terms to be included in this list):

- Shortness of breath (dyspnea)
- Cough
- Chronic Cough
- Respiratory infections
- Chronic Respiratory Infections
- Cachexia (weight loss not considered cachexia by investigators, not included)
- Bone pain (if stage IV with distal metastases)
- Fever (if stage IV or symptom of infection)
- Paraneoplastic syndromes. Paraneoplastic syndromes can include but are not limited to myasthenic syndrome (AB to muscles); hypercalcemia; SIADH, Horner's syndrome if a pancoast tumor and muscle weakness of the hands resulting from invasion of the brachial plexus.
- Loss of appetite

12.4 Retrospective PGx Substudy

INTRODUCTION

PGx research aims to provide information regarding how naturally occurring changes in a subject's gene and/or expression based on genetic variation may impact what treatment options are best suited for the subject. Through investigation of PGx by technologies such as genotyping, gene sequencing, statistical genetics and Genome-Wide Association Studies (GWAS), the relationship between gene profiles and a drug's kinetics, efficacy or toxicity may be better understood. As many diseases may be influenced by 1 or more genetic variations, PGx research may identify which genes are involved in determining the way a subject may or may not respond to a drug.

OBJECTIVES

The PGx research that may be conducted in the future with acquired blood samples is exploratory. The objective of this research will be to analyze or determine genes of relevance to clinical response, pharmacokinetics and toxicity/safety issues.

By analyzing genetic variations, it may be possible to predict an individual subject's response to treatment in terms of efficacy and/or toxicity.

SUBJECT PARTICIPATION

Subjects who have consented to participate in this study may participate in this PGx substudy. As part of this substudy, subjects must provide separate written consent prior to providing any blood samples that may be used at a later time for genetic analysis.

SAMPLE COLLECTION AND STORAGE

Subjects who consent to participate in this substudy will provide one 4-mL tube of blood per Astellas' instructions. Each sample will be identified by the unique subject number (first code). Samples will be shipped frozen to a designated banking CRO either directly from site or via a central laboratory as directed by Astellas.

PGx ANALYSIS

Details on the potential PGx analysis cannot be established yet. Astellas may initiate the PGx analysis in case evidence suggests that genetic variants may be influencing the drug's kinetics, efficacy and/or safety. Prior to initiating any analysis on the banked samples, the Astellas Research Ethic Committee (AREC) must approve the analysis plan.

DISPOSAL OF PGx SAMPLES/DATA

All PGx samples collected will be stored for a period of up to 15 years following study database hard lock. If there is no requirement for analysis, the blood sample will be destroyed after the planned storage period. The subject has the right to withdraw consent at any time. When a subject's withdraw notification is received, the PGx sample will be destroyed. The results of any PGx analysis conducted on a sample prior to its withdrawal will be retained at Astellas indefinitely.

INFORMATION DISCLOSURE TO THE SUBJECTS

The PGx substudy may be conducted following the conclusion of the clinical study, if applicable. The results of the genetic analysis will not be provided to any investigators or subjects, nor can the results be requested at a later date. Any information that is obtained from the PGx analysis will be the property of Astellas.

12.5 FACT-EGFRI-18

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

		Not at all	A little bit	Some -what	Quite a bit	Very much
ST4	My skin or scalp feels irritated	0	1	2	3	4
ST5	My skin or scalp is dry or "flaky"	0	1	2	3	4
ST6	My skin or scalp itches	0	1	2	3	4
ST7	My skin bleeds easily	0	1	2	3	4
ST9	I am bothered by a change in my skin's sensitivity to the sun	0	1	2	3	4
ST32	My skin condition interferes with my ability to sleep	0	1	2	3	4
ST22	My skin condition affects my mood	0	1	2	3	4
ST17	My skin condition interferes with my social life	0	1	2	3	4
ST24	I am embarrassed by my skin condition	0	1	2	3	4
ST37	I avoid going out in public because of how my skin looks	0	1	2	3	4
ST26	I feel unattractive because of how my skin looks	0	1	2	3	4
ST34	Changes in my skin condition make daily life difficult	0	1	2	3	4
ST38	The skin side effects from treatment have interfered with household tasks	0	1	2	3	4
ST16	My eyes are dry	0	1	2	3	4
ST15	I am bothered by sensitivity around my fingernails or toenails	0	1	2	3	4
ST29	Sensitivity around my fingernails makes it difficult to perform household tasks	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
ST11	I am bothered by increased facial hair	0	1	2	3	4

12.6 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

12.7 EORTC-QLQ-30

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

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
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

12.8 EQ-5D-5L

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

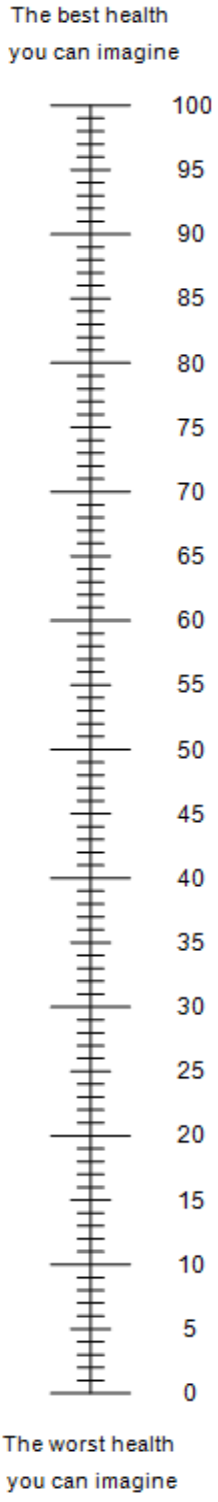
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



12.9 RECIST V1.1

Table 1 – Time point response: patients with target (+/– non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Table 2 – Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.

a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Table 3 – Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.
a If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Reproduced from: Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-247

12.10 ECOG Performance Status

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Reproduced from: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-55

12.11 Laboratory Assessments

Laboratory tests will be performed predose according to the Schedule of Assessments and sent to a central laboratory for analysis.

Panel/Assessment	**Parameters to be analyzed**
Hematology	Hematocrit (Hct) Hemoglobin (Hgb) Red Blood Cell Count (RBC) White Blood Cell Count (WBC) WBC differential Platelets Mean Corpuscular Volume (MCV) Mean Corpuscular Hemoglobin (MCH) Mean Corpuscular Hemoglobin Concentration (MCHC)
Biochemistry (fasting)	Sodium (Na) Magnesium (Mg) Creatine Phosphokinase (CK) Potassium (K) Calcium (Ca) Corrected Serum Calcium Chloride (Cl) Phosphate (P) Creatinine (Cr) Glucose (Gl) Blood Urea Nitrogen (BUN) Alkaline Phosphatase (ALP) Aspartate Aminotransferase (AST) Alanine Aminotransferase (ALT) Lactate Dehydrogenase (LDH) Bilirubin Total (TBL) (total and direct) Total Protein (TP) Albumin (Alb) Bicarbonate (HCO3) Serum HCG for female subjects of childbearing potential Serum osmolality
Urinalysis	Protein Glucose pH Occult Blood Ketones Bilirubin Urobilinogen Sodium Potassium Chloride Urine osmolality
Coagulation Profile	PT (sec) APTT INR

13 ATTACHMENT 1: SUBSTANTIAL AMENDMENT 1

I. The purpose of this amendment is:

Substantial Changes
1. Revise Study Secondary Objectives
DESCRIPTION OF CHANGE:
Duration of Response (DOR) is added as a secondary endpoint and Quality of Life (QoL) is moved from an exploratory to a secondary endpoint.
RATIONALE:
DOR and QoL are both important clinical endpoints. Adding these 2 endpoints as secondary endpoints will not affect the analysis of the primary and key secondary endpoints for the following reasons: (1) the Hochberg procedure is used to control the key secondary endpoints of overall survival (OS) and overall response rate (ORR) (2) only when the primary endpoint significantly favors the ASP8273 arm will the secondary endpoints be tested.
2. Increase Planned Sample Size
DESCRIPTION OF CHANGE:
The sample size of this study is increased from 540 to 600 patients and the total number of study centers is increased from 200 to 240 centers. Revisions are made accordingly to the number of events required for interim and final analysis.
RATIONALE:
Based on the mechanism of action of ASP8273 and available clinical data, it is likely that the separation of progression free survival (PFS) curves will occur late in Study 9287-CL-0302. As this study is the single pivotal study for registration, the sample size is increased to 600 patients to make sure that the study has adequate power if late separation occurs.
3. Clarify the Method of Comparator Selection
DESCRIPTION OF CHANGE:
Additional description is added to clarify that sites will choose one comparator to be used for all subjects at their site, rather than choosing for each individual subject during screening
RATIONALE:
In order to ensure consistency throughout the study and to limit potential bias in comparator choice. Potential bias may occur if the comparator is chosen after review of a potential study participant's clinical profile.
4. Update Imaging Requirements

DESCRIPTION OF CHANGE:
Adding imaging of the brain as a requirement for all subjects at baseline.
RATIONALE:
Non-small cell lung cancer (NSCLC) commonly metastasizes to the brain. Based on this patient population and to ensure that progression is accurately determined post-baseline, brain imaging is to be done at baseline to document the presence or absence of metastatic lesions to the brain.
5. Update Contraception Requirements
DESCRIPTION OF CHANGE:
Revisions are made to the text for contraception requirements to more clearly define acceptable versus highly effective birth control methods.
RATIONALE:
As requested by several European Regulatory/Ethics committees, to be consistent with the EU Heads of Medicines Agency (HMA) Clinical Trial Facilitation Group (CTFG) guidelines.
6. Clarify Study Eligibility Criteria
DESCRIPTION OF CHANGE:
Revisions are made to inclusion/exclusion criteria to provide additional clarity on epidermal growth factor receptor (EGFR) testing, measurable lesion requirements and previous treatment.
RATIONALE:
Clarifying language is added to further explain these eligibility requirements based on frequently received questions to date.
7. Update Dose Modification Guidelines
DESCRIPTION OF CHANGE:
Dose modification guidelines are updated to include specific guidance for events of suspected or confirmed interstitial lung disease (ILD), ocular toxicities and hepatic impairment for all study drugs. Explicit guidelines for gefitinib based on severity grade are added. Clarification on interruption duration is added. Guidance for ASP8273 dose modification is updated to allow re-escalation of the dose.
RATIONALE:
Updates to dose reduction/interruption guidelines are made consistent with the commitment in the response to FDA comments to include this in the upcoming amendment. The instruction for ASP8273 de-escalation/re-escalation are revised based on experience to date in the early phase studies. Guidance to minimize the drug interruption duration is added based on data on disease progression following drug interruption in the early phase studies.

8. Provide Additional Clarification for Criteria For Treatment After Progression
DESCRIPTION OF CHANGE:
Criteria are added that must be met to allow subjects to continue protocol-assigned treatment after documentation of radiological progressive disease. More detailed guidance is added for determining progression at the next radiographic assessment.
RATIONALE:
Updates are made consistent with current practice per NCCN guideline in alignment with current standard of care for treatment after progression, as well as per the commitment in the response to FDA comments to include this in the upcoming amendment.
9. Update Concomitant Medication Restrictions
DESCRIPTION OF CHANGE:
Revisions are made to the concomitant medication restrictions for ASP8273, erlotinib and gefitinib to provide more details around toxicity management of interstitial lung disease, ocular toxicity and hepatotoxicity.
RATIONALE:
Updates are made to ensure consistency with current package insert for the commercial comparator products. In addition, fluconazole is a moderate CYP3A4 inhibitor according to the FDA guideline, and therefore should not be listed as strongly prohibited. The protocol text is being updated to be consistent with Appendix 12.1 which is correct.

Non-substantial Changes
1. Update Sponsor contact information
DESCRIPTION OF CHANGE:
Provide current key sponsor contact information and update serious adverse event (SAE) reporting details for Japan.
RATIONALE:
Update to reflect changes to the global medical lead and clinical research study team and addition of [redacted] contract research organization (CRO) support for SAE processing in Japan.
2. Revision of Study Drug Storage Requirements
DESCRIPTION OF CHANGE:
Storage requirements are updated for erlotinib and gefitinib.
RATIONALE:
To be consistent with commercial and study labeling for comparator study drugs.

3. Minor administrative-type corrections and clarifications
DESCRIPTION OF CHANGE:
Other minor corrections, e.g., typographical errors, formatting, clarifications, deletions.
RATIONALE:
To ensure accuracy and clarity throughout protocol based on errors discovered and questions received on the protocol to date.

II. Amendment Summary of Changes: Substantial

IV Synopsis, Study Objective, Endpoints for Evaluation and 2 Study Objective(s), Design, and Endpoints *2.1.2 Secondary Objectives, 2.1.3 Exploratory Objectives, 2.3.2 Secondary Endpoints and 2.3.3 Exploratory Endpoints*
WAS:
2.1.2 Secondary Objectives • Overall survival (OS) • Overall response rate (ORR) as assessed by IRR • PFS as assessed by the investigator • Disease control rate (DCR) as assessed by IRR • Safety of ASP8273 2.1.3 Exploratory Objectives • To evaluate potential biomarkers that may affect treatment outcome • Evaluation of the pharmacokinetics of ASP8273 • To evaluate the impact of subsequent therapy on progression free survival on next-line therapy (PFS#2) • To evaluate Quality of Life (QoL) and patient-reported outcome (PRO) parameters as measured by FACT-EGFRI-18, EORTC-QLQ-LC13, EORTC-QLQ-C30 and EQ-5D-5L 2.3.2 Secondary Endpoints • OS • Best overall response rate (CR + PR) by IRR • PFS by the investigator • Disease control rate (CR+PR+SD) by IRR • Safety variables (e.g., AEs, laboratory tests, vital sign measurements, ECGs) 2.3.3 Exploratory Endpoints • Plasma T790M and other biomarkers related to EGFR TKI sensitivity and/or resistance • Plasma pharmacokinetics of ASP8273 • PFS#2 on subsequent therapy • QoL and PRO parameters

IS AMENDED TO:
2.1.2 Secondary Objectives • Overall survival (OS) • Overall response rate (ORR) as assessed by IRR • PFS as assessed by the investigator • Disease control rate (DCR) as assessed by IRR • **Duration of Response (DOR) as assessed by IRR** • Safety of ASP8273 • **To evaluate Quality of Life (QoL) and patient-reported outcome (PRO) parameters as measured by FACT-EGFRI-18, EORTC-QLQ-LC13, EORTC-QLQ-C30 and EQ-5D-5L** 2.1.3 Exploratory Objectives • To evaluate potential biomarkers that may affect treatment outcome • Evaluation of the pharmacokinetics of ASP8273 • To evaluate the impact of subsequent therapy on progression free survival on next-line therapy (PFS#2) • ~~To evaluate Quality of Life (QoL) and patient-reported outcome (PRO) parameters as measured by FACT-EGFRI-18, EORTC-QLQ-LC13, EORTC-QLQ-C30 and EQ-5D-5L.~~ 2.3.2 Secondary Endpoints • OS • Best overall response rate (CR + PR) by IRR • PFS by the investigator • Disease control rate (CR+PR+SD) by IRR • **DOR by IRR** • Safety variables (e.g., AEs, laboratory tests, vital sign measurements, ECGs) • **QoL and PRO parameters** 2.3.3 Exploratory Endpoints • Plasma T790M and other biomarkers related to EGFR TKI sensitivity and/or resistance • Plasma pharmacokinetics of ASP8273 • PFS#2 on subsequent therapy • ~~QoL and PRO parameters~~

IV Synopsis, Planned Total Number of Study Centers and Location(s)
WAS:
Approximately 200 centers (Globally)
IS AMENDED TO:
Approximately ~~200~~ **240** centers (Globally)

IV Synopsis, Number of Subjects to be Enrolled/Randomized, Study Design Overview, Sample Size Justification, Interim Analysis, 2 Study Objective(s), Design, and Endpoints and 7 Statistical Methodology *2.2.1 Study Design, 7.1 Sample Size and 7.9 Interim Analysis*
WAS:
Approximately 540 subjects
IS AMENDED TO:
Approximately ~~540~~ **600** subjects

IV Synopsis, Study Design Overview and 2 Study Objective(s), Design, and Endpoints *2.2.1 Study Design*
WAS:
PFS by IRR is the primary variable. Secondary variables include OS, ORR, PFS by the investigator, DCR and safety. Exploratory variables include biomarkers, pharmacokinetics, PFS #2 on subsequent therapy and QoL/PRO. Arm A will receive 300 mg daily of ASP8273 and Arm B will receive either 150 mg erlotinib or 250 mg gefitinib daily, as decided by the investigator prior to randomization. Both arms will follow 28-day cycles of continuous dosing. Subjects will be stratified according to the following: ECOG PS (0, 1 or 2), EGFR mutation status (exon 19 deletion or mutations in exon 21 [L858R]), TKI chosen (erlotinib or gefitinib) and race (Asian versus non-Asian).
IS AMENDED TO:
PFS by IRR is the primary variable. Secondary variables include OS, ORR, PFS by the investigator, DCR**, DOR,** ~~and~~ safety **and QoL/PRO**. Exploratory variables include biomarkers, pharmacokinetics~~,~~ **and** PFS #2 on subsequent therapy ~~and QoL/PRO~~. Arm A will receive 300 mg daily of ASP8273 and Arm B will receive either 150 mg erlotinib or 250 mg gefitinib daily, as decided by the investigator ~~prior to randomization~~ **for each site at the beginning of the trial**. Both arms will follow 28-day cycles of continuous dosing. Subjects will be stratified according to the following: ECOG PS (0, 1 or 2), EGFR mutation status (exon 19 deletion or mutations in exon 21 [L858R]), TKI chosen (erlotinib or gefitinib) and race (Asian versus non-Asian).

IV Synopsis, Study Design Overview, 2 Study Objective(s), Design, and Endpoints and 5 Treatments and Evaluation *2.2.1 Study Design and 5.3 Efficacy Assessment*
ADDED:
Imaging of the brain is required at baseline for all subjects, and may be repeated throughout the study as clinically indicated. If a brain lesion not previously irradiated is selected as a target lesion at baseline, the assessment should be repeated at all subsequent imaging timepoints.

IV Synopsis, Study Design Overview, Sample Size Justification, 2 Study Objective(s), Design, and Endpoints and 7 Statistical Methods

2.2.1 Study Design, 7.1 Sample size and 7.4.1.1 Primary Analysis

WAS:

An independent Data Monitoring Committee (IDMC) will be chartered to oversee safety and the planned futility analysis which will occur after at least 181 PFS events have been observed.

The primary analysis will occur when at least 362 PFS#1 events are observed which is expected to occur approximately 36 months after randomization. Primary endpoint, secondary endpoints and other endpoints will be analyzed at the time of primary analysis.

Assuming HR=0.667 (median PFS in Arm A and Arm B are 15.6 months and 10.4 months, respectively), a total of 362 PFS events will provide approximately 95% power to detect a statistically significant difference at type I error rate of 1-sided 0.025.

IS AMENDED TO:

An independent Data Monitoring Committee (IDMC) will be chartered to oversee safety and the planned **interim** futility analysis which will occur after at least ~~181~~ **210** PFS**#1** events have been observed.

The primary analysis will occur when at least ~~362~~ **420** PFS#1 events are observed which is expected to occur approximately 36 months after randomization **of the first subject**. Primary endpoint, secondary endpoints and other endpoints will be analyzed at the time of primary analysis.

Assuming HR=0.667 (median PFS in Arm A and Arm B are 15.6 months and 10.4 months, respectively), a total of ~~362~~ **420** PFS events will provide approximately ~~95~~**98.7**% power to detect a statistically significant difference at type I error rate of 1-sided 0.025.

IV Synopsis, Inclusion/Exclusion Criteria and 3 Study Population

3.2 Inclusion Criteria No. 4, 7, 13 and 14

WAS:

4. Female subject must either:
   - Be of nonchildbearing potential:
     - postmenopausal (defined as at least 1 year without any menses) prior to Screening, or
     - documented surgically sterile
   - Or, if of childbearing potential:
     - Agree not to try to become pregnant during the study and for 28 days after the final study drug administration
     - And have a negative serum pregnancy test at Screening
     - And, if heterosexually active, agree to consistently use 2 forms of highly effective birth control* (at least 1 of which must be a barrier method) starting at Screening and throughout the study period and for 28 days after the final study drug administration

7. Male subject and their female spouse/partners who are of childbearing potential must be using highly effective contraception consisting of 2 forms of birth control* (1 of which must be a barrier method) starting at Screening and continue throughout the study period and for 90 days after the final study drug administration.
*Highly effective forms of birth control include:
- Consistent and correct usage of established oral, injected or implanted hormonal methods of contraception
- Established intrauterine device (IUD) or intrauterine system (IUS)
- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository (not applicable in Japan)
- Calendar-based contraceptive methods (Knaus-Ogino or rhythm method [Japan only])

13. Subject has an EGFR activating mutation (exon 19 deletion or exon 21 L858R), with or without T790M mutation, by local or central testing on examination of a NSCLC FFPE specimen. A tissue sample from the same block used to determine eligibility by local testing should be available to send to the central lab for confirmatory testing.

14. Subject must have at least 1 measureable lesion based on RECIST V1.1.

IS AMENDED TO:

4. Female subject must either:
- Be of nonchildbearing potential:
  - postmenopausal (defined as at least 1 year without any menses) prior to Screening, or
  - documented surgically sterile
- Or, if of childbearing potential:
  - Agree not to try to become pregnant during the study and for 28 days after the final study drug administration
  - And have a negative serum pregnancy test at Screening
  - And, if heterosexually active, agree to consistently use 2 forms of ~~highly effective~~ birth control* (at least 1 of which must be a **highly effective method* and one must be a** barrier method) starting at Screening and throughout the study period and for 28 days after the final study drug administration

7. Male subject and their female spouse/partners who are of childbearing potential must be using highly effective contraception consisting of 2 forms of birth control* (1 of which must be a barrier method) starting at Screening and continue throughout the study period and for 90 days after the final study drug administration.
*Highly effective forms of birth control include:
- Consistent and correct usage of established oral, injected or implanted hormonal methods of contraception
- Established intrauterine device (IUD) or intrauterine system (IUS)

***Acceptable forms of birth control include:**
- Barrier methods of contraception: condom or occlusive cap (diaphragm or

cervical/vault caps) with spermicidal foam/gel/film/cream/suppository (not applicable in Japan~~)~~ **and Thailand: with spermicidal foam/gel/film/cream/suppository)**
- Calendar-based contraceptive methods (Knaus-Ogino or rhythm method [Japan **and Thailand** only])

13. Subject has an EGFR activating mutation (exon 19 deletion or exon 21 L858R), with or without T790M mutation, by local or central testing on examination of a NSCLC FFPE specimen **(archival or fresh biopsy) Subjects harboring both exon 19 deletion and exon 21 L858R mutations are not eligible**. A tissue sample from the same block used to determine eligibility by local testing should be available to send to the central lab for confirmatory testing. **Subjects randomized based on local results indicating presence of EGFR mutations may remain on study if central results are discordant.**

14. Subject must have at least 1 measureable lesion based on RECIST V1.1. **Previously irradiated lesions will not be considered as measurable lesions.**

IV Synopsis, Inclusion/Exclusion Criteria and 3 Study Population

3.3 Exclusion Criteria No. 1, 5, 19 and 21

WAS:

1. Subject has received intervening anticancer treatment or previous treatment with chemotherapy for metastatic disease. The administration of neoadjuvant or adjuvant chemotherapy is allowed as long as it has finalized ≥ 6 months before the first dose of study drug.

5. Subject has symptomatic central nervous system (CNS) metastasis. Subject with previously treated brain or CNS metastases are eligible provided that the subject has recovered from any acute effects of radiotherapy and is not requiring escalating doses of steroids, and any whole brain radiation therapy was completed at least 2 weeks prior to study drug administration, or any stereotactic radiosurgery (SRS) was completed at least 1 week prior to the first dose of study drug.

19. Subject has another malignancy which requires treatment.

21. Subject has used the following drugs:
    a. Potent CYP 3A4 inhibitors within 7 days prior to first dose of study drug
    b. Proton pump inhibitors such as omeprazole within 14 days prior to first dose of study drug

IS AMENDED TO:

1. Subject has received intervening anticancer treatment or previous treatment with chemotherapy for metastatic disease **other than palliative local radiation to painful bone metastases completed at least 1 week prior to the first dose of study drug**. The administration of neoadjuvant or adjuvant chemotherapy is allowed as long as it has finalized ≥ 6 months before the first dose of study drug.

5. Subject has symptomatic central nervous system (CNS) metastasis. Subject with previously treated brain or CNS metastases are eligible provided that the subject has

recovered from any acute effects of radiotherapy**, does not have brain metastasis related symptoms,** ~~and~~ is not requiring ~~escalating doses of~~ **systemic** steroids~~,~~ **for at least 2 weeks prior to study drug administration,** and any whole brain radiation therapy was completed at least ~~2~~ **4** weeks prior to study drug administration~~,~~ or any stereotactic radiosurgery (SRS) was completed at least ~~1~~ **2** week**s** prior to the first dose of study drug. **Steroid inhaler use or ointment treatment for other concomitant medical disease is permitted.**

19. Subject has another **past or active** malignancy which requires treatment. **Prior carcinoma in situ or non-melanoma skin cancer after curative resection are permitted.**

21. Subject has ~~used~~ **received** ~~the following drugs:a. Potent~~ **potent** CYP 3A4 inhibitors within 7 days prior to first dose of study drug ~~b.~~ or ~~Proton~~ **proton** pump inhibitors such as omeprazole within 14 days prior to first dose of study drug

IV Synopsis, Comparative Drug(s) Dose(s)
WAS:
Erlotinib 150 mg once daily or gefitinib 250 mg once daily as decided by the investigator.
IS AMENDED TO:
Erlotinib 150 mg once daily or gefitinib 250 mg once daily as decided by the investigator **for each site at the beginning of the trial**.

IV Synopsis, Dose Modifications and 5 Treatments and Evaluation

5.1.2 Increase or Reduction in Dose of the Study Drug(s) and 5.1.2.1 ASP8273 Dose Modification

WAS:

5.1.2 Increase or Reduction in Dose of the Study Drug(s)

Dosing for ASP8273, erlotinib or gefitinib may be interrupted or reduced (ASP8273 and erlotinib only) for any event if the investigator deems it necessary to ensure subject safety. The subject may be discontinued from treatment if there is an interruption of treatment for > 14 days despite optimal treatment of side effects. A discussion with the Medical Monitor should occur to confirm if the subject should continue on study treatment.

5.1.2.1 ASP8372 Dose Modification

If a grade 3 or 4 study drug-related toxicity persists or recurs after 2 dose reductions, the subject should be permanently discontinued from ASP8273 treatment. Dose reescalation in subjects who had a dose reduction is not permitted. Additionally, if after resolution of a Grade 4 event requiring dose interruption and/or dose reduction, the event reoccurs at a G3 or higher the subject should be permanently discontinued from ASP8273.

Table 3 ASP8273 Dose Modification

Dose level	ASP8273 dose (mg qd)
Starting dose	300
-1	200
-2	100

IS AMENDED TO:

5.1.2 Increase or Reduction in Dose of the Study Drug(s)

Dosing for ASP8273, erlotinib or gefitinib may be interrupted or reduced (ASP8273 and erlotinib only) for any event if the investigator deems it necessary to ensure subject safety. **Subjects requiring a treatment interruption should be re-evaluated not longer than 7 days from initial interruption and restarted on study drug as soon as clinically stable.** The subject may be discontinued from treatment if there is an interruption of treatment for > 14 **consecutive** days despite optimal treatment of side effects. A discussion with the Medical Monitor should occur to confirm if the subject should continue on study treatment.

In the event of acute onset or worsening of pulmonary symptoms likely suggestive of interstitial lung disease (dyspnea, cough, fever), study drug should be interrupted and a prompt investigation of these symptoms should occur and appropriate treatment initiated. If ILD is confirmed, study drug should be discontinued, and the subject should be treated appropriately per local standard of care.

Study drug should be interrupted if the subject experiences eye toxicity such as acute and severe eye pain or keratitis. Subjects with suspected keratitis should have study drug withheld until recovery and discontinued for persistent severe keratitis. Subjects with ocular toxicities should be evaluated by an ophthalmologist.

If the subject experiences severe hepatic impairment, study drug should be discontinued and the subject should be treated appropriately per local standard of care.

5.1.2.1 ASP8372 Dose Modification

Subjects requiring a dose reduction may be re-escalated one dose level (i.e., subjects reduced to 100 mg may only be re-escalated to 200 mg). If the event leading to the reduction recurs, the subject should be reduced to the lower dose level and not re-escalated again. If a grade 3 or 4 study drug-related toxicity persists or recurs after 2 dose reductions, the subject should be permanently discontinued from ASP8273 treatment. ~~Dose reescalation in subjects who had a dose reduction is not permitted.~~ Additionally, if after resolution of a Grade 4 event requiring dose interruption and/or dose reduction, the event reoccurs at a G3 or higher the subject should be permanently discontinued from ASP8273.

Table 3 ASP8273 Dose Modification

Dose level	ASP8273 dose (mg qd)
Starting dose	300
-1	200
-2	100

IV Synopsis, Dose Modifications and 5 Treatments and Evaluation

5.1.2.2 Erlotinib Dose Modification

WAS:

Dose modifications for erlotinib will be implemented for toxicities of ILD, skin rash, and diarrhea. Subjects requiring dose reduction of erlotinib may have the dose reescalated if they have been on a stable dose for ≥ 3 weeks without further toxicities requiring dose modification and it is considered by the investigator to be in the best interest of the subject. If any toxicity requiring dose interruption of erlotinib recurs despite the initial dose reduction to

level -1 (100 mg qd), erlotinib may be reduced again to level -2 (50 mg qd). If 2 levels of erlotinib dose reduction are required, subsequent reescalation may only be to dose level -1.

Table 6 Events Requiring Erlotinib Dose Modification

Erlotinib Dose Modification Criteria	
Toxicity (NCI CTCAE v4.03)	Dose Modification[1] for Erlotinib
Diarrhea	
Grade 1 or 2	None. Initiate therapy with antidiarrhea medication as needed
Grade 3[2] or 4[2]	Interrupt erlotinib until resolution to ≤ grade 2 and then restart 1 dose level lower
Rash	
Grade 1	None
Grade 2	None. If rash persists and is intolerable or worsens over 10-14 days, then reduce by 1 dose level and initiate treatment as outlined in protocol.
Grade 3[2]	Reduce by 1 dose level. If rash persists or worsens over 10-14 days, then interrupt erlotinib until resolution to ≤ grade 2 and then restart 1 dose level lower.
Grade 4	Permanently discontinue erlotinib
Interstitial Lung Disease	
Any Grade	If ILD is suspected, erlotinib should be interrupted immediately pending diagnostic evaluation. If ILD is diagnosed, erlotinib should be discontinued permanently and appropriate treatment instituted as necessary.
Other Toxicities	
Grade 1 or 2	None
Grade 3 [2, 3]	Interrupt erlotinib until resolution to ≤ grade 2 and then restart 1 dose level lower
Grade 4	Permanently discontinue erlotinib

IS AMENDED TO:

Dose modifications for erlotinib are suggested for toxicities of ILD, skin rash, and diarrhea, however the locally approved label for erlotinib dose modification for toxicities should be followed. ~~Dose modifications for erlotinib will be implemented for toxicities of ILD, skin rash, and diarrhea~~. Subjects requiring dose reduction of erlotinib may have the dose ~~reescalated~~ **re-escalated** if they have been on a stable dose for ≥ 3 weeks without further toxicities requiring dose modification and it is considered by the investigator to be in the best interest of the subject. If any toxicity requiring dose interruption of erlotinib recurs despite the initial dose reduction to level -1 (100 mg qd), erlotinib may be reduced again to level -2 (50 mg qd). If 2 levels of erlotinib dose reduction are required, subsequent reescalation may only be to dose level -1.

Treatment with erlotinib should be used with extra caution in subjects with total bilirubin > 3 x ULN. Erlotinib dosing should be interrupted or discontinued if changes in liver function are severe such as doubling of total bilirubin and/or tripling of transaminases in the setting of pretreatment values outside normal range. In the setting of worsening liver function tests, before they become severe, dose interruption and/or dose reduction with frequent liver function test monitoring should be considered. Erlotinib dosing should be interrupted or discontinued if total bilirubin is > 3 x ULN and/or transaminases are > 5 x ULN in the setting of normal pretreatment value.

Table 6 Events Requiring Erlotinib Dose Modification

Erlotinib Dose Modification Criteria	
Toxicity (NCI CTCAE v4.03)	Dose Modification[1] for Erlotinib
Diarrhea	
Grade 1 or 2	None. Initiate therapy with antidiarrhea medication as needed
Grade 3[2] or 4[2]	Interrupt erlotinib until resolution to ≤ grade 2 and then restart 1 dose level lower
Rash	
Grade 1	None
Grade 2	None. If rash persists and is intolerable or worsens over 10-14 days, then reduce by 1 dose level and initiate treatment as outlined in protocol.
Grade 3[2]	Reduce by 1 dose level. If rash persists or worsens over 10-14 days, then interrupt erlotinib until resolution to ≤ grade 2 and then restart 1 dose level lower.
Grade 4	Permanently discontinue erlotinib
Interstitial Lung Disease	
Any Grade	If ILD is suspected, erlotinib should be interrupted immediately pending diagnostic evaluation. If ILD is diagnosed, erlotinib should be discontinued permanently and appropriate treatment instituted as necessary.
Other Toxicities**, including ocular toxicity**	
Grade 1 or 2	None
Grade 3 [2, 3]	Interrupt erlotinib until resolution to ≤ grade 2 and then restart 1 dose level lower
Grade 4	Permanently discontinue erlotinib

IV Synopsis, Dose Modifications and 5 Treatments and Evaluation

5.1.2.3 Gefitinib Dose Modification

WAS:

There will be no dose reductions for subjects receiving gefitinib. Below summarizes recommended therapy interruption for gefitinib.

Subjects with poorly tolerated diarrhea (sometimes associated with dehydration) or skin adverse drug reactions may be successfully managed by providing a brief (up to 14 days) therapy interruption followed by reinstatement of the 250 mg daily dose.

In the event of acute onset or worsening of pulmonary symptoms (dyspnea, cough, fever), gefitinib therapy should be interrupted (up to 14 days) and a prompt investigation of these symptoms should occur and appropriate treatment initiated. If ILD is confirmed, gefitinib should be discontinued, and the subject treated appropriately.

IS AMENDED TO:

There will be no dose reductions for subjects receiving gefitinib **as it is only available as a single strength tablet**. Below summarizes recommended therapy interruption for gefitinib**; however, the locally approved label should be followed for additional guidance.**

~~Subjects with poorly tolerated diarrhea (sometimes associated with dehydration) or skin adverse drug reactions may be successfully managed by providing a brief (up to 14 days) therapy interruption followed by reinstatement of the 250 mg daily dose.~~

~~In the event of acute onset or worsening of pulmonary symptoms (dyspnea, cough, fever), gefitinib therapy should be interrupted (up to 14 days) and a prompt investigation of these~~

~~symptoms should occur and appropriate treatment initiated. If ILD is confirmed, gefitinib should be discontinued, and the subject treated appropriately.~~

Gefitinib Dose Modification Criteria	
Toxicity (NCI CTCAE v4.03)	**Dose Modification for Gefitinib**
Diarrhea	
Persistent Grade 2 or ≥ Grade 3	**Interrupt gefitinib up to 14 days. Resume treatment when event resolves to Grade ≤ 1 or baseline.**
Skin Reactions	
≥ Grade 3	**Interrupt gefitinib up to 14 days. Resume treatment when event resolves to Grade ≤ 1 or baseline.**
Interstitial Lung Disease	
Any Grade	**In the event of acute onset or worsening of pulmonary symptoms suggestive of ILD (dyspnea, cough, fever), gefitinib should be interrupted immediately pending diagnostic evaluation. If ILD is confirmed, gefitinib should be discontinued permanently and appropriate treatment instituted as necessary.**
AST, ALT or bilirubin elevation	
≥ Grade 2	**Interrupt gefitinib up to 14 days. Resume treatment when event resolves to Grade ≤ 1 or baseline.**
Other Toxicities, including ocular toxicity	
≥ Grade 3	**Interrupt gefitinib up to 14 days. Resume treatment when event resolves to Grade ≤ 1 or baseline.**

If ILD, persistent severe keratitis, severe hepatic impairment or gastrointestinal perforation is confirmed, gefitinib should be discontinued, and the subject **should be** treated appropriately **per local standard of care**.

IV Synopsis, Discontinuation Criteria and 6 Discontinuation

6.1 Discontinuation of Individual Subject(s)

WAS:

The subject will be discontinued from the treatment period if any of the following occur:

- Subject develops radiological progressive disease (i.e., PFS#1) per RECIST v1.1 based on central confirmation of investigator assessment
    - If there is radiographic evidence of PD but the investigator believes the subject is continuing to derive clinical benefit from study drug, the subject may remain on study drug until the next scheduled radiographic assessment.
    - If the next radiographic assessment confirms PD per RECIST v1.1, then the subject must be discontinued from study drug.

IS AMENDED TO:

The subject will be discontinued from the treatment period if any of the following occur:

- Subject develops radiological progressive disease (i.e., PFS#1) per RECIST v1.1 based on central confirmation of investigator assessment
    - If there is radiographic evidence of PD ~~but~~ **by investigator, however** the investigator believes the subject is continuing to derive clinical benefit **(asymptomatic and/or without worsening of performance status or overall**

health) from study drug, **and an increase in tumor burden is not likely to affect vital organ function,** the subject may remain on study drug until the next scheduled radiographic assessment **which should occur after 56 days (± 7 days)**.
  - If the next radiographic assessment ~~confirms~~ **indicates** PD per RECIST 1.1**, which is confirmed by the central reviewer**, then the subject must be discontinued from study drug.
  - **In the rare event where PD suspected on initial assessment is not confirmed on subsequent scan by the investigator or central reviewer, the subject may continue in the study.**
  - **The investigator should make every effort to immediately submit radiographic assessments for central review when PD is either suspected or confirmed or uncertainty exists.**
  - **In case of PD determination by the investigator, however not confirmed by the central reviewer, and subject is progressing clinically and requires new anti-cancer treatment immediately, the subject should be discontinued.**
- **Subject is required to receive local or systemic anti-cancer treatment based on investigator's clinical opinion.**

IV Synopsis, Concomitant Medication Restrictions or Requirements and 5 Treatments and Evaluation

5.1.3 Previous and Concomitant Treatment (Medication and Nonmedication Therapy)

WAS:

Arm A (ASP8273)

The following medications/food are likely to influence evaluation of the safety, pharmacokinetics or efficacy of ASP8273 and will be strictly prohibited:

	Prohibited Medications/Food	**Reason to Exclude**
1	Chemotherapy, radiotherapy, immunotherapy, or other medications intended for antitumor activity	Likely affect efficacy, safety or pharmacokinetics of ASP8273
2	Investigational products or therapy other than ASP8273	
3	Potent inhibitors (e.g., ketoconazole, fluconazole, grapefruit or grapefruit juice) or inducers (e.g., rifampin, phenytoin or St. John's wort) of CYP3A4	ASP8273 is a substrate of CYP3A4
4	CYP3A4 and/or P-gp substrates with a narrow therapeutic index[1]	ASP8273 may be an inhibitor of CYP3A4 and/or P-gp

Arm B (Erlotinib/Gefitinib)

The following medications/food are likely to influence evaluation of the safety, pharmacokinetics or efficacy of erlotinib/gefitinib, and will be strictly prohibited:

Prohibited Medications/Food		Reason to Exclude
All Subjects	Chemotherapy, radiotherapy, immunotherapy, or other medications intended for antitumor activity other than erlotinib/gefitinib	Likely affect efficacy, safety or pharmacokinetics of erlotinib or gefitinib
	Investigational products or therapy	

	Potent inhibitors (e.g., ketoconazole, fluconazole, grapefruit or grapefruit juice) or inducers (e.g., rifampin, phenytoin or St. John's wort) of CYP3A4	Erlotinib and gefitinib are substrates of CYP3A4
	Proton pump inhibitors or drugs that cause significant elevation in gastric pH	Elevation in gastric pH may reduce bioavailability of erlotinib or gefitinib
Subjects receiving erlotinib	Potent/moderate inhibitors of CYP1A2	Erlotinib is a substrate of CYP1A2

The use of the following medications should be avoided or used with caution and closely monitored:

Medications to be Avoid or Used with Caution		Reason to be Cautious
All Subjects	Moderate/weak inhibitors or inducers of CYP3A4	Erlotinib and gefitinib are substrates of CYP3A4
Subjects receiving gefitinib	Potent inhibitors of CYP2D6	Gefitinib is a substrate of CYP2D6
	CYP2D6 substrates with narrow therapeutic index[1]	Gefitinib is an inhibitor of CYP2D6
	Warfarin	INR elevations and/or bleeding events have been noted in subjects taking warfarin while on gefitinib therapy
	Vinorelbine	Vinorelbine taken concomitantly with gefitinib may exacerbate neutropenia

IS AMENDED TO:

Arm A (ASP8273)

The following medications/food are likely to influence evaluation of the safety, pharmacokinetics or efficacy of ASP8273 and will be strictly prohibited:

	Prohibited Medications/Food	**Reason to Exclude**
1	Chemotherapy, radiotherapy, immunotherapy, or other medications intended for antitumor activity	Likely affect efficacy, safety or pharmacokinetics of ASP8273
2	Investigational products or therapy other than ASP8273	
3	Potent inhibitors (e.g., ketoconazole, ~~fluconazole,~~ grapefruit or grapefruit juice) or inducers (e.g., rifampin, phenytoin or St. John's wort) of CYP3A4	ASP8273 is a substrate of CYP3A4
4	CYP3A4 and/or P-gp substrates with a narrow therapeutic index[1]	ASP8273 may be an inhibitor of CYP3A4 and/or P-gp

Arm B (Erlotinib/Gefitinib)

The following medications/food are likely to influence evaluation of the safety, pharmacokinetics or efficacy of erlotinib/gefitinib, and will be strictly prohibited:

Prohibited Medications/Food		Reason to Exclude
All Subjects	Chemotherapy, radiotherapy, immunotherapy, or other medications intended for antitumor activity other than erlotinib/gefitinib	Likely affect efficacy, safety or pharmacokinetics of erlotinib or gefitinib

	Investigational products or therapy	
	Potent inhibitors (e.g., ketoconazole, ~~fluconazole~~, grapefruit or grapefruit juice) or inducers (e.g., rifampin, phenytoin or St. John's wort) of CYP3A4	Erlotinib and gefitinib are substrates of CYP3A4
	Proton pump inhibitors or drugs that cause significant elevation in gastric pH	Elevation in gastric pH may reduce bioavailability of erlotinib or gefitinib
~~Subjects receiving erlotinib~~	~~Potent/moderate inhibitors of CYP1A2~~	~~Erlotinib is a substrate of CYP1A2~~
The use of the following medications should be avoided or used with caution and closely monitored:		
Medications to be Avoid**ed** or Used with Caution		Reason to be Cautious
All Subjects	Moderate/weak inhibitors or inducers of CYP3A4	Erlotinib and gefitinib are substrates of CYP3A4
	Inhibitors or inducers of P-gp	**Erlotinib and gefitinib are substrates of P-gp**
	Warfarin	**INR elevations and/or bleeding events have been noted in subjects taking warfarin while on gefitinib therapy**
Subjects receiving erlotinib	**Potent inhibitors of CYP1A2**	**Erlotinib is a substrate of CYP1A2**
Subjects receiving gefitinib	Potent inhibitors of CYP2D6	Gefitinib is a substrate of CYP2D6
	CYP2D6 substrates with narrow therapeutic index[1]	Gefitinib is an inhibitor of CYP2D6
	~~Warfarin~~	~~INR elevations and/or bleeding events have been noted in subjects taking warfarin while on gefitinib therapy~~
	~~Vinorelbine~~	~~Vinorelbine taken concomitantly with gefitinib may exacerbate neutropenia~~

IV Synopsis, Statistical Methods, Efficacy
WAS:
The Full Analysis Set (FAS) will be used for the primary efficacy analysis. All subjects who are randomized will be included in the FAS. For time to event endpoints including PFS and OS, log-rank test stratified by ECOG PS (0 and 1 combined versus 2), EGFR mutation status (exon 19 deletion or mutations in exon 21 [L858R]), TKI chosen (erlotinib versus gefitinib) will be used to compare the 2 treatment arms. The hazard ratio and corresponding 95% confidence interval from the stratified Cox proportional hazards regression model will also be presented. The median survival function will be estimated using the Kaplan-Meier method and will be reported along with the corresponding 95% confidence interval by treatment arm.

IS AMENDED TO:
The Full Analysis Set (FAS) will be used for the primary efficacy analysis. All subjects who are randomized will be included in the FAS. For time to event endpoints including PFS**,** ~~and~~ OS, **and DOC,** log-rank test stratified by ECOG PS (0 and 1 combined versus 2), EGFR mutation status (exon 19 deletion or mutations in exon 21 [L858R]), TKI chosen (erlotinib versus gefitinib) will be used to compare the 2 treatment arms. The hazard ratio and corresponding 95% confidence interval from the stratified Cox proportional hazards regression model will also be presented. The median survival function will be estimated using the Kaplan-Meier method and will be reported along with the corresponding 95% confidence interval by treatment arm.

IV Synopsis, Interim Analyses and 7 Statistical Methods *7.9 Interim Analysis (and Early Discontinuation of the Clinical Study)*
WAS:
An interim futility analysis is planned to occur after 181 PFS events are observed, which is expected to occur approximately 20 months after the first subject is randomized. If the observed HR is less than 1.1, recruitment into the study will continue as planned until 540 subjects are recruited. The interim analysis will be conducted by the IDMC. In addition safety data reviews during the trial will be conducted by the IDMC on a periodic basis. For example, the IDMC will review safety data after the first 50 patients have been treated. The full procedures for IDMC safety review will be described in a separate IDMC charter.
IS AMENDED TO:
An interim futility analysis is planned to occur after ~~181~~ **210** PFS events are observed, which is expected to occur approximately 2~~0~~**2** months after the first subject is randomized. If the observed HR is less than 1.1, recruitment into the study will continue as planned until ~~540~~ **600** subjects are recruited. The interim analysis will be conducted by the IDMC. In addition safety data reviews during the trial will be conducted by the IDMC on a periodic basis. For example, the IDMC will review safety data after the first 50 patients have been ~~treated~~ **randomized and on study drug for approximately 3 months**. The full procedures for IDMC safety review will be described in a separate IDMC charter.

V Flow Chart and Schedule of Assessments, Table 1 Schedule of Assessments *Footnote 10*
WAS:
9 Image assessments will be done every 56 days (± 7 days), scheduled in a way to allow results to be available for the odd cycle day 1 visit (i.e., prior to cycles 3, 5, 7, 9 etc.). CT scan with contrast (chest and abdomen) is the preferred modality for tumor assessment. MRI is acceptable if local standard practice or if CT scans are contraindicated in a subject

(e.g., subject is allergic to contrast media). All other RECIST-approved scanning methods such as X-ray are optional. PET-CT scans must use contrast. To ensure comparability, the screening and subsequent assessment of response should be performed using identical techniques. The same method should be employed and assessed by the same individual on each occasion if possible. For subjects with known brain metastases at study entry, it is recommended that repeat imaging also include the brain and the same methods used to detect brain lesions at baseline are to be used to follow the lesions throughout the study. Confirmation scans for CR or PR should be done at the next scheduled assessment. A chest x-ray or other appropriate imaging of the lungs should be performed in addition to specified imaging time points if a subject develops symptoms suggestive of ILD.

IS AMENDED TO:

~~9~~**10** Image assessments will be done every 56 days (± 7 days), scheduled in a way to allow results to be available for the odd cycle day 1 visit (i.e., prior to cycles 3, 5, 7, 9 etc.). **Imaging of the brain is required at baseline for all subjects, and may be repeated throughout the study as clinically indicated. If a brain lesion is selected as a target lesion at baseline, the assessment should be repeated at all subsequent imaging timepoints.** CT scan with contrast (chest and abdomen) is the preferred modality for tumor assessment. MRI is acceptable if local standard practice or if CT scans are contraindicated in a subject (e.g., subject is allergic to contrast media). All other RECIST-approved scanning methods such as X-ray are optional. PET-CT scans must use contrast. To ensure comparability, the screening and subsequent assessment of response should be performed using identical techniques. The same method should be employed and assessed by the same individual on each occasion if possible. ~~For subjects with known brain metastases at study entry, it is recommended that repeat imaging also~~ **Imaging assessments, including brain, should utilized** ~~include the brain and~~ the same methods ~~used to detect brain lesions at baseline are to be used to follow the lesions~~ throughout the study. Confirmation scans for CR or PR should be done at the next scheduled assessment. A chest x-ray or other appropriate imaging of the lungs should be performed in addition to specified imaging time points if a subject develops symptoms suggestive of ILD.

3 Study Population

3.1 Selection of Study Population

WAS:

First-line subjects with locally advanced, metastatic or unresectable stage IIIB/IV adenocarcinoma NSCLC (newly diagnoses or recurrent) with EGFR activating mutations (exon 19 deletion or exon 21 L858R) will be selected for this study.

IS AMENDED TO:

First-line subjects with locally advanced, metastatic or unresectable stage IIIB/IV adenocarcinoma NSCLC (newly diagnoses or recurrent) with EGFR activating mutations (exon 19 deletion or exon 21 L858R) will be selected for this study. **Subjects who have both an exon 19 deletion and exon 21 L858R mutation will not be included.**

4 Treatment(s)

4.5 Assignment and Allocation

WAS:

Randomization in a 1:1 ratio to each of the 2 treatment arms will be performed via Interactive Response Technology (IRT). Randomization will be stratified by ECOG PS (0, 1 or 2), EGFR mutation type (exon 19 deletion or mutation in exon 21 L858R), TKI chosen (erlotinib versus gefitinib) and race (Asian versus nonAsian). During screening for each subject the site will need to designate in IRT if the subject will receive erlotinib or gefitinib in the event they are randomized to the comparator arm. Prior to the initiation of the study treatment, the site staff will contact the IRT in order to determine the randomly assigned treatment arm. Specific procedures for randomization through the IRT are contained in the study procedures manual.

IS AMENDED TO:

Randomization in a 1:1 ratio to each of the 2 treatment arms will be performed via Interactive Response Technology (IRT). Randomization will be stratified by ECOG PS (0, 1 or 2), EGFR mutation type (exon 19 deletion or mutation in exon 21 L858R), TKI chosen (erlotinib versus gefitinib) and race (Asian versus nonAsian). **At the beginning of the trial, prior to site initiation and shipment of study drug supplies, each investigator will select either erlotinib or gefitinib to be utilized for all subjects randomized to** ~~During screening for each subject the site will need to designate in IRT if the subject will receive erlotinib or gefitinib in the event they are randomized to~~ the comparator arm **at their site**. Prior to the initiation of the study treatment, the site staff will contact the IRT in order to determine the randomly assigned treatment arm. Specific procedures for randomization through the IRT are contained in the study procedures manual.

5 Treatments and Evaluation

5.1.2.1 ASP8273 Dose Modification, Table 4

WAS:

Table 4 Events Requiring ASP8283 Dose Modification

Hyponatremia	
Grade 1	• Recheck serum sodium levels as clinically indicated • In addition, urine osmolality, serum osmolality, and urine sodium concentrations should also be measured as clinically indicated • Dosing may continue without interruption at the discretion of the investigator
Grade 3	• For serum sodium levels < 130 – 125 mmol/L dosing may continue at the discretion of the investigator with additional monitoring as noted below • For serum sodium levels < 125 mm/L interrupt dosing • Serum sodium levels, serum osmolality, urine osmolality and urine sodium concentrations should be measured to determine the etiology of the hyponatremia and continue to be drawn as clinically indicated until the serum sodium levels recover ≤ Grade 1 or baseline • Consider fluid management plan if clinically indicated at the discretion of the

	investigator • Dosing should be held until serum sodium levels recover to ≤ Grade 1 or baseline, then dosing my resume, at the discretion of the investigator, at 1 dose level lower
Other adverse events	
IS AMENDED TO:	
Hyponatremia	
Grade 1	• Recheck serum sodium levels as clinically indicated • In addition, urine osmolality, serum osmolality, and urine sodium concentrations should also be measured as clinically indicated • Dosing may continue without interruption at the discretion of the investigator
Grade 2	• **Not defined by NCI CTCAE v4.3**
Grade 3	• For serum sodium levels < 130 – 125 mmol/L dosing may continue at the discretion of the investigator with additional monitoring as noted below • For serum sodium levels < 125 mm/L interrupt dosing • Serum sodium levels, serum osmolality, urine osmolality and urine sodium concentrations should be measured to determine the etiology of the hyponatremia and continue to be drawn as clinically indicated until the serum sodium levels recover ≤ Grade 1 or baseline • Consider fluid management plan if clinically indicated at the discretion of the investigator • Dosing should be held until serum sodium levels recover to ≤ Grade 1 or baseline, then dosing my resume, at the discretion of the investigator, at 1 dose level lower • **If Grade > 3 hyponatremia recurs after resuming ASP8273 at a reduced dose, ASP8273 may be discontinued**
Interstitial Lung Disease	
Any grade	• **If ILD is suspected, ASP8273 should be interrupted immediately pending diagnostic evaluation. If ILD is diagnosed, ASP8273 should be discontinued permanently and appropriate treatment instituted as necessary.**
Other adverse events**, including ocular toxicity**	

7 Statistical Methodology

Section 7.4.2.5 Duration of Response (DOR) and 7.4.2.6 QoL and PRO Parameters

ADDED:

7.4.2.5 Duration of Response (DOR)

DOR is defined as the time from the date of the first response CR/PR (whichever is first recorded) as assessed by IRR to the date of radiographic progression or date of censoring. If a subject has not progressed, the subject will be censored at the date of last radiological assessment or at the date of first CR/PR if no post-baseline radiological assessment is available.

The distribution of DOR will be estimated for each treatment arm using Kaplan-Meier methodology and compared between Arm A and Arm B using the log-rank test stratified by ECOG PS (0 and 1 combined versus 2), EGFR mutation type (exon 19 deletion or mutations in exon 21 [L858R]) and TKI chosen (erlotinib versus gefitinib).

In addition, stratified Cox proportional hazard model will be used to estimate the hazard ratio and the corresponding 95% confidence interval.

7.4.2.6 QoL and PRO Parameters

Descriptive QoL and PRO analyses will be performed on the FAS. Completion rate for each questionnaire will be summarized. Additional analyses will be discussed in details in the statistical analysis plan.

7 Statistical Methods

7.4.3.1 PFS on Next-Line Therapy (PFS#2)

WAS:

PFS on next-line therapy is defined as the time from randomization to objective tumor progression on next-line therapy (second progression), discontinuation of next-line treatment, or death from any cause, whichever comes first.

Patients alive and for whom a second objective disease progression has not been observed should be censored at the last time known to be alive and without second objective disease progression.

IS AMENDED TO:

PFS**#2** ~~on next-line therapy~~ is defined as the time from ~~randomization~~ **initiation of new systemic anti-cancer treatment (excluding local radiation, surgical removal of metastatic site or protocol defined Erlotinib or Geftinib or ASP8273 based on initial treatment allocation per subject) to investigator-determined progression, discontinuation of new treatment, start of a different treatment or death from any cause, whichever comes first. Otherwise, subjects will be censored.**
~~to objective tumor progression on next-line therapy (second progression), discontinuation of next-line treatment, or death from any cause, whichever comes first.~~

Subjects who have not started new systemic anti-cancer treatment will be censored at Day 1. Subjects who are alive, started new systemic anti-cancer treatment and for whom a PFS#2 event has not been observed should be censored at the last time known to be alive.
~~Patients alive and for whom a second objective disease progression has not been observed should be censored at the last time known to be alive and without second objective disease progression.~~

7 Statistical Methods

7.4.3.2 Other Exploratory Analyses

DELETED

~~In addition, analysis will be performed to evaluate Quality of Life (QoL) and PRO parameters as measured by FACT-EGFR-TKI, EORTC-QLQ-LC13, EORTC-QLQ-C30 and EQ-5D-5L.~~

12 Appendices

12.1 List of Excluded Concomitant Medications

WAS:

The following medications/food are likely to influence evaluation of the safety, pharmacokinetics or efficacy of ASP8273 or erlotinib/gefitinib, and will be strictly prohibited:

Arm A (ASP8273)	Arm B (Erlotinib/Gefitinib)
• Chemotherapy, radiotherapy, immunotherapy or other medications intended for antitumor activity. • Investigational products or therapy other than ASP8273. • Potent inhibitors or inducers of CYP3A4 • CYP3A4 and/or P-gp substrates with a narrow therapeutic index	• Chemotherapy, radiotherapy, immunotherapy or other medications intended for antitumor activity other than erlotinib/gefitinib. • Investigational products or therapy. • Potent inhibitors or inducers of CYP3A4 • Proton pump inhibitors or drugs that cause significant elevation in gastric pH • For subjects who are administrated with erlotinib: o Potent/moderate inhibitors of CYP1A2

Examples for excluded inhibitors, inducers and substrates for enzymes and transporters are provided below. This list should NOT be considered all inclusive. Investigators will consult individual drug labels to determine liability of the drugs.

Excluded CYP Inhibitors/Inducers

CYP3A4	Inhibitors	Potent: boceprevir, clarithromycin, conivaptan, grapefruit juice*, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole *The effect of grapefruit juice varies widely among brands and is concentration-, dose- and preparation dependent.
	Inducers	Potent: avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort
CYP1A2	Inhibitors	Potent: ciprofloxacin, enoxacin, fluvoxamine Moderate: methoxsalen, mexiletine, oral contraceptives, phenylpropanolamine, thiabendazole, vemurafenib, zileuton

IS AMENDED TO:

The following medications/food are likely to influence evaluation of the safety, pharmacokinetics or efficacy of ASP8273 or erlotinib/gefitinib, and will be strictly prohibited:

Arm A (ASP8273)	Arm B (Erlotinib/Gefitinib)
• Chemotherapy, radiotherapy,	• Chemotherapy, radiotherapy, immunotherapy or

immunotherapy or other medications intended for antitumor activity. • Investigational products or therapy other than ASP8273. • Potent inhibitors or inducers of CYP3A4 • CYP3A4 and/or P-gp substrates with a narrow therapeutic index	other medications intended for antitumor activity other than erlotinib/gefitinib. • Investigational products or therapy. • Potent inhibitors or inducers of CYP3A4 • Proton pump inhibitors or drugs that cause significant elevation in gastric pH ~~• For subjects who are administrated with erlotinib:~~ ~~○ Potent/moderate inhibitors of CYP1A2~~

Examples for excluded inhibitors, inducers and substrates for enzymes and transporters are provided below. This list should NOT be considered all inclusive. Investigators will consult individual drug labels to determine liability of the drugs.

Excluded CYP Inhibitors/Inducers		
CYP3A4	Inhibitors	Potent: boceprevir, clarithromycin, conivaptan, grapefruit juice*, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole *The effect of grapefruit juice varies widely among brands and is concentration-, dose- and preparation dependent.
	Inducers	Potent: avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort
~~CYP1A2~~	~~Inhibitors~~	~~Potent: ciprofloxacin, enoxacin, fluvoxamine~~ ~~Moderate: methoxsalen, mexiletine, oral contraceptives, phenylpropanolamine, thiabendazole, vemurafenib, zileuton~~

II Summary of Changes: Non-substantial

II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

24h-Contact for Serious Adverse Events (SAEs), Medical Expert and Clinical Research Contacts

	WAS:
24h-Contact for Serious Adverse Events (SAEs) See [Section 5.5]	[redacted], MD, PhD [redacted] Astellas Pharma Global Development, Inc. [redacted] Please fax the SAE Worksheet to: Astellas Pharma Global Development, Inc. [redacted]

	[redacted] For Japan: [redacted] – Japan [redacted]
Medical Expert:	[redacted], MD, PhD [redacted] Astellas Pharma Global Development, Inc. 1 Astellas Way, Northbrook, Illinois 60062 [redacted]
Clinical Research Contacts:	NA/EU/LA: [redacted] Astellas Pharma Global Development, Inc. 1 Astellas Way, Northbrook, Illinois 60062 [redacted]
IS AMENDED TO:	
24h-Contact for Serious Adverse Events (SAEs) See [Section 5.5]	[redacted], MD~~, PhD~~ [redacted] Astellas Pharma Global Development, Inc. [redacted] Please fax the SAE Worksheet to: Astellas Pharma Global Development, Inc. [redacted] For Japan: [redacted] [redacted] – Japan [redacted]

Medical Expert:	[redacted] Astellas Pharma Global Development, Inc. 1 Astellas Way, Northbrook, Illinois 60062 [redacted]
Clinical Research Contacts:	~~NA/EU/LA:~~ [redacted] ~~Astellas Pharma Global Development, Inc.~~ ~~1 Astellas Way, Northbrook, Illinois 60062~~ [redacted]

1 Introduction

1.3.1 ASP8273

WAS:

In ongoing Study 8273-CL-0101, 12 subjects experienced DLTs (100 mg group, n = 1; 400 mg group, n = 7; 600 mg group, n = 4). Diarrhoea was the most common DLT, occurring in 4 subjects. Nausea, hyponatraemia and colitis each occurred in 2 subjects, while the rest of the DLTs occurred in 1 subject each.

IS AMENDED TO:

In ongoing Study 8273-CL-0101, ~~12~~ **9** subjects experienced DLTs (~~100 mg group, n = 1;~~ 400 mg group, n = ~~7~~ **5**; 600 mg group, n = 4). Diarrhoea was the most common DLT, occurring in **4 3** subjects. Nausea~~, hyponatraemia~~ and colitis each occurred in 2 subjects, while the rest of the DLTs occurred in 1 subject each.

4 Treatment(s)

4.1.2 Comparative Drug(s)

WAS:

Erlotinib will be provided as oral tablets in 150, 100 and 25 mg strengths in bottles containing 30 tablets each. Erlotinib should be stored at room temperature, not above 25°C (77°F).

Gefitinib will be provided as oral tablets in 250 mg strength in blister packs containing 30 tablets each. Gefitinib should be stored at room temperature between 20°C and 25°C (68-77°F).

IS AMENDED TO:

Erlotinib will be provided as oral tablets in 150, 100 and 25 mg strengths in bottles containing 30 tablets each. Erlotinib should be stored at room temperature, ~~not above~~ 25°C (77°F) **with excursions permitted to 15° to 30°C (59-86°F).**
Gefitinib will be provided as oral tablets in 250 mg strength in blister packs containing 30 tablets each. Gefitinib should be stored at room temperature between ~~20~~ **1**°C and ~~25~~ **30**°C (~~68~~ **33.8** ~~77~~ **86**°F).

5 Treatments and Evaluation

5.5.5 Reporting of Serious Adverse Events (SAEs)

WAS:

Please fax or email the SAE worksheet for Japan (JUTOKUNA YUUGAIJISHOU HOUKOKUSHO) to:

[redacted] – Japan

[redacted]

IS AMENDED TO:

Please fax or email the SAE worksheet for Japan (JUTOKUNA YUUGAIJISHOU HOUKOKUSHO) to:

[redacted]

or

[redacted] – Japan

[redacted]

8 Operational and Administrative Considerations

8.1.7 End of Trial in All Participating Countries

WAS:

The end of trial in all participating countries may be defined as the Last Subject's Last Visit, or at the discretion of the sponsor.

IS AMENDED TO:

~~The end of trial in all participating countries may be defined as the Last Subject's Last Visit, or at the discretion of the sponsor.~~

The study completion is defined as the conclusion of data collection for the defined study endpoints. Subjects continuing to derive clinical benefit are allowed to continue to receive treatment in the study after study completion. The end of study in all participating countries is therefore defined as the Last Subject's Last Visit, or last contact. The study may be closed within a participating country per local regulations after the study has completed if all subjects enrolled in the country are no longer receiving study treatment.

14 SPONSOR'S SIGNATURES

ELECTRONIC SIGNATURE PAGE

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