TIGER-1: A Randomized, Open-label, Phase 2/3 Study of CO-1686 or Erlotinib as First-line Treatment of Patients with EGFR-Mutant Advanced/Metastatic Non-small Cell Lung Cancer (NSCLC)

Protocol Number:	CO-1686-022
Investigational Product:	CO-1686
IND Number:	[redacted]
EUDRA CT Number:	[redacted]
Development Phase:	Phase 2/3
Indication Studied:	Locally advanced or metastatic NSCLC with mutant epidermal growth factor receptor (EGFR)
Sponsor Name and Address:	Clovis Oncology, Inc. 5500 Flatiron Parkway, Suite 100 Boulder, CO 80301 USA Phone Number: 303-625-5000 Facsimile Number: 303-245-0360
Responsible Medical Officer:	[redacted]
Compliance Statement:	This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, clinical research guidelines established by the Code of Federal Regulations (Title 21, CFR Parts 50, 56, and 312), and International Conference on Harmonisation (ICH) Good Clinical Practices (GCP) Guidelines. Essential study documents will be archived in accordance with applicable regulations.

[redacted]

[redacted]

CONFIDENTIALITY STATEMENT

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Protocol Approval Signature Page

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[redacted]

Protocol Acceptance Form

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Title: TIGER-1: A Randomized, Open-label, Phase 2/3 Study of CO-1686 or Erlotinib as First-line Treatment of Patients with EGFR-Mutant Advanced/Metastatic Non-small Cell Lung Cancer (NSCLC)

Date: [redacted]

Version: [redacted]

Reviewed and Approved by:

I have carefully read this protocol and agree that it contains all of the necessary information required to conduct this study. I agree to conduct this study as described and according to the Declaration of Helsinki, ICH Guidelines for GCP, and all applicable regulatory requirements.

Investigator's Signature | Date

Name (printed)

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1 SYNOPSIS

Protocol Number	CO-1686-022
Title	TIGER-1: A Randomized, Open-label, Phase 2/3 Study of CO-1686 or Erlotinib as First-line Treatment of Patients with EGFR-Mutant Advanced/Metastatic Non-small Cell Lung Cancer (NSCLC)
Phase	Phase 2/3
Introduction	In mid-2015, Clovis submitted a New Drug Application for the use of CO-1686 in patients with T790M-positive NSCLC. In June 2016, the FDA issued a Complete Response Letter to Clovis stating that more data are required to approve CO-1686 for use outside of a clinical trial. Based on this outcome, Clovis decided to discontinue development of CO-1686 for NSCLC. Patients will be informed of this change in the development plans in an update to the informed consent form for this study. Those patients who continue to derive clinical benefit from study treatment, will be allowed to continue on study at the discretion of the Principal Investigator in an extension phase. The purpose of this protocol amendment is to add a new Extension Phase to allow patients to continue on study but to avoid unnecessary collection of data that will no longer be analyzed or required for regulatory purposes, whilst maintaining an appropriate level of safety monitoring. A new schedule of assessments for the Extension Phase as well as a complete description of procedures is provided in Appendix D. This schedule replaces all schedules of assessments in Section 9 Study Procedures and should be followed for all patients. An important change of the Extension phase is the removal of the option for patients to crossover to CO-1686 following radiographic progression on erlotinib. The decision to remove the crossover option to CO-1686 was based on the recommendation of the Data Monitoring Committee (DMC), which oversees the risk/benefit aspects of the study. Patients and their physicians are directed to seek alternative treatments, which can fulfill this need. For patients who wish to continue CO-1686 or erlotinib treatment post progression, it is important that a full exploration of alternative treatment options between patients and their treating physicians takes place prior to making that decision. In addition, this amendment also introduces the availability of NAT2 testing for patients, an indirect indicator of the likelihood of developing hyperglycaemia or QTc prolongation. The availability and disclosure of this information to the patients's treating physician will not affect the monitoring and associated treatment guidelines for these adverse events. Investigators and their staff are directed to the current Investigator's Brochure for the most current efficacy and safety data, in which integrated summaries of the latest available data can be found and supersedes all safety and efficacy data in this protocol.

	CO-1686 is a novel, potent, small molecule irreversible tyrosine kinase inhibitor (TKI) that selectively targets mutant forms of the epidermal growth factor receptor (EGFR) while sparing wild-type (WT) EGFR. Activating EGFR mutations are key drivers of NSCLC in 10% to 15% of patients of European descent and approximately 30% of patients of Asian descent.[1] Patients with the most common activating EGFR mutations, exon 21 L858R and deletions in exon 19 (del19), typically have good responses to therapy with first-generation EGFR-TKIs such as erlotinib or gefitinib and also with the second generation inhibitor afatinib.[2-4] Toxicity associated with erlotinib, gefitinib, and afatinib includes skin rash and diarrhea related to inhibition of the WT EGFR in skin and intestine, respectively.[5-7] Despite an impressive initial response, disease progression generally occurs after 9 to 14 months of EGFR-TKI therapy. In an estimated 50% to 60% of these cases, the resistance to current EGFR-TKIs is believed to be driven by an additional EGFR mutation in exon 20 called T790M (the "gatekeeper" mutation).[8-10] There are no approved therapies that target T790M specifically, and standard of care remains cytotoxic chemotherapy. Yu et al reported that T790M positive (T790M+) disease is fatal, with a median overall survival (OS) of less than 2 years.[10] Furthermore, a small group of mutant EGFR NSCLC patients (~2% to 3%) will exhibit T790M mutations in tumors at baseline (so-called "*de novo*" T790M disease) and these patients are known to have very poor outcomes on standard TKI therapy.[11,12] Some of these patients may have germline T790M mutations, and they typically develop clinical lung cancer only when a classical "activating "mutation (such as L858R or del19) occurs as a second hit.[13] Nonclinical data demonstrate that CO-1686 inhibits T790M as well as the common activating mutations (L858R, del19) and has minimal inhibitory activity towards WT-EGFR at therapeutic doses. It is anticipated that CO-1686 will promote tumor cell death with the common activating mutations as well as the T790M mutation providing therapeutic benefit in patients with minimal toxicities driven by WT-EGFR. In addition, CO-1686 caused tumor regression *in vivo* as a first-line agent in mouse models harboring primary EGFR mutations. In Study CO-1686-008 patients with advanced EGFR mutation-positive NSCLC and previous treatment with an EGFR inhibitor are being treated in expansion cohorts with doses of 500 mg, 625 mg or 750 mg twice daily (BID). Response Evaluation Criteria in Solid Tumors (RECIST)[14] responses have been observed across these doses of CO-1686, and the objective response rate (ORR) in patients with T790M+ NSCLC is 55%. The median progression-free survival (PFS) in these patients receiving CO-1686 monotherapy in the context of acquired resistance to initial TKI had not been reached with the current estimate exceeding 1 year. The most common toxicity observed is hyperglycemia, occurring in approximately 30% of patients, which is generally managed with oral anti-hyperglycemic therapy. Adverse events (AEs) typical of WT-EGFR inhibition (the combination of rash and chronic diarrhea) have not been observed with CO-1686. The compelling clinical activity and manageable safety profile demonstrated in the CO-1686-008 study provide a strong rationale for investigating whether CO-1686 may achieve better activity than standard of care agents in first-line treatment of advanced EGFR mutated NSCLC, driven by inhibition of the initial activating EGFR mutation and suppression of T790M emergence.

	The objectives of Study CO-1686-022 (known as TIGER-1) are to compare the antitumor efficacy of oral single-agent CO-1686 to erlotinib when administered as a first-line targeted treatment to patients with EGFR-mutated, advanced/metastatic NSCLC and to assess the safety and tolerability of CO-1686 in this population. Efficacy will be measured primarily by PFS. Secondary efficacy measures will include patient reported outcomes (PRO), RECIST response rate, duration of response (DR), and OS (although control arm crossover may limit the utility of the OS data). Relative benefit of CO-1686 versus erlotinib will specifically be studied in *de novo* T790M+ patients. This study will also compare the treatment effects of CO-1686 and erlotinib on surrogate markers that may be predictive of disease progression and evaluate possible predictive biomarkers.
Planned Number of Patients	In the Phase 2 part, 200 patients will be randomized 1:1 to either CO-1686 500 mg BID or erlotinib 150 mg once daily (QD). In the Phase 3 part, up to 1,000 additional patients will be randomized 1:1 to either CO-1686 500 mg BID or erlotinib 150 mg QD into a single (sponsor)-blinded part of this clinical study.
Planned Number of Sites	Approximately 95 investigative sites will be open globally.
Study Objectives	**Primary Objective** • To compare the antitumor efficacy of oral single-agent CO-1686 with that of erlotinib as measured by PFS, when administered as a first-line targeted treatment to patients with EGFR-mutated, advanced/metastatic NSCLC **Secondary Objectives** • To compare secondary measures of clinical efficacy (ORR, DR, and OS) of oral single-agent CO-1686 with that of erlotinib when administered as a first-line targeted treatment in patients with advanced/metastatic NSCLC whose tumors have EGFR-activating mutations • To assess PFS, ORR, DR, and OS in patients with baseline T790M mutations based on central allele-specific polymerase chain reaction (PCR) EGFR mutation assay • To assess quality of life (QOL) using the PRO of European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) and the EORTC Quality of Life Questionnaire Lung Cancer module (EORTC QLQ-LC13),[15] the Dermatology Life Quality Index (DLQI),[16] and the EQ-5D instrument[17] in patients receiving treatment with CO-1686 versus erlotinib • To evaluate safety and tolerability of CO-1686 versus erlotinib in patients with advanced/metastatic NSCLC whose tumors have EGFR-activating mutations • To determine pharmacokinetics (PK) of CO-1686 in this patient population using population PK (POPPK) methods and explore correlations between PK, exposure, response, and/or safety findings

	Exploratory Objectives • To compare disease control rate (DCR) of oral single-agent CO-1686 with that of erlotinib when administered as a first-line targeted treatment in patients with advanced/metastatic NSCLC whose tumors have EGFR-activating mutations • To assess DCR in patients with baseline T790M mutations based on central allele-specific PCR EGFR mutation assay • To compare kinetics of tumor growth between treatment arms measured by rate of change in sum of the longest diameters of target lesions (SLD) or rate of change of estimated or measured assessments of tumor volume • To compare efficacy between treatment arms in patients with baseline T790M+ disease, detected using an ultra-sensitive research assay • To compare the effect between treatment arms in patients who develop progressive disease (PD) while on study treatment but continue to receive assigned study treatment with CO-1686 or erlotinib beyond progression • To evaluate concordance of EGFR mutation detection between patient tissue and plasma and to assess CO-1686 or erlotinib mediated alterations in levels of EGFR mutation detected using circulating tumor DNA (ctDNA) obtained from patient plasma • To explore tissue and blood-based biomarkers that may be predictive of response or primary resistance to CO-1686 or erlotinib and investigate mechanisms of acquired resistance to treatment with CO-1686 or erlotinib using patient tumor tissue and blood samples
Study Endpoints	**Primary Endpoints** • PFS according to RECIST Version 1.1 as determined by investigator review (invPFS) **Secondary Endpoints** • ORR, and DR, according to RECIST Version 1.1 as determined by investigator review, and OS • invPFS, ORR, DR, and OS in patients with baseline T790M mutations confirmed by central EGFR mutation assay • Change from baseline in QOL as measured using the PRO of EORTC QLQ-C30, EORTC QLQ-LC13, the DLQI, and the EQ-5D following treatment with CO-1686 versus erlotinib • Treatment-emergent AEs, laboratory abnormalities, and electrocardiogram (ECG) abnormalities • Plasma PK parameters for CO-1686 based on sparse sampling **Exploratory Endpoints** • DCR according to RECIST Version 1.1 as determined by investigator review • DCR in patients with baseline T790M mutations confirmed by central EGFR mutation assay

	• Rate of change in SLD • Rate of change in tumor volume (measured or modeled) • InvPFS, ORR, DR, DCR, time-to-treatment failure, and OS in patients who develop PD while on study treatment but continue to receive assigned study treatment with CO-1686 or erlotinib beyond progression • Concordance of tumor and plasma ctDNA mutational analysis using contemporaneous samples • Time from randomization to second observed increase over nadir in plasma mutant EGFR ctDNA levels (activating mutation, T790M mutation, either or both) • Fraction of patients exhibiting disappearance of mutant EGFR ctDNA after initiating treatment with CO-1686 • Change from baseline in other tissue and blood biomarkers associated with the EGFR signaling pathways and relationship with clinical efficacy outcomes
Study Design	In mid-2015, Clovis submitted a New Drug Application for the use of CO-1686 in patients with T790M-positive NSCLC. In June 2016, the FDA issued a Complete Response Letter to Clovis stating that more data are required to approve CO-1686 for use outside of a clinical trial. Based on this outcome, Clovis decided to discontinue development of CO-1686 for NSCLC. Patients will be informed of this change in the development plans in an update to the informed consent form for this study. Those patients who continue to derive clinical benefit from study treatment, will be allowed to continue on study at the discretion of the Principal Investigator in an extension phase. The purpose of this protocol amendment is to add a new Extension Phase to allow patients to continue on study but to avoid unnecessary collection of data that will no longer be analyzed or required for regulatory purposes, whilst maintaining an appropriate level of safety monitoring. A new schedule of assessments for the Extension Phase as well as a complete description of procedures is provided in Appendix D. This schedule replaces all schedules of assessments in Section 9 Study Procedures and should be followed for all patients. An important change of the Extension phase is the removal of the option for patients to crossover to CO-1686 following radiographic progression on erlotinib. The decision to remove the crossover option to CO-1686 was based on the recommendation of the DMC, which oversees the risk/benefit aspects of the study. Patients and their physicians are directed to seek alternative treatments, which can fulfill this need. For patients who wish to continue CO-1686 or erlotinib treatment post progression, it is important that a full exploration of alternative treatment options between patients and their treating physicians takes place prior to making that decision. This is a randomized Phase 2/3 study of CO-1686 versus erlotinib as a first-line treatment for patients with advanced/metastatic NSCLC whose tumors have EGFR-activating mutations. The study will consist of Phase 2 and Phase 3 parts which will use the same enrollment criteria and treatment assignment principles.

	The Phase 2 part is an open-label study; in the Phase 3 part, the sponsor will be blinded to efficacy and safety results aggregated by randomized treatment group. The Phase 2 part will enroll approximately 200 patients. Data from the Phase 2 part will be used to inform on the sample size in the Phase 3 part of the study. The sample size of the Phase 3 component will be capped at approximately 1,000 patients. The Phase 3 part will include up to 3 interim analyses. At each interim analysis, enrollment into the Phase 3 part may be stopped if there is a high probability of success in the Phase 3 part of the study. If enrollment is stopped early, the Phase 3 part of study will continue until at least 70% of the randomized patients have a PFS event. Patients will be randomized 1:1 to erlotinib or CO-1686 and the randomization will be stratified based on sensitizing EGFR mutation (L858R, del19, or other) and territory of residence at time of randomization (Asia vs. non-Asia). The study will consist of a screening phase to establish study eligibility (including tumor genotype) and document baseline measurements; a treatment phase, in which patients will receive either CO-1686 500 mg BID or erlotinib 150 mg QD to ascertain safety and efficacy until radiographically confirmed disease progression; and a follow-up phase, to monitor PFS, survival status and subsequent NCSLC cancer therapy. In the Phase 2 part only, patients initially randomized to erlotinib may be eligible to participate in an optional crossover phase to receive CO-1686 if they demonstrate the T790M resistance mutation after radiographic progression on erlotinib treatment among other eligiblity requirements. Patients who progress on erlotinib who have not developed the T790M mutation will not be eligible to receive CO-1686 in the crossover portion of the study, because for these patients, progression on erlotinib is likely driven by other mechanisms that are unlikely to respond to CO-1686. Treatment with CO-1686 or erlotinib is continuous, unless delayed or reduced according to protocol-specified toxicity criteria. Protocol-specified treatment will continue until radiographically confirmed PD according to RECIST Version 1.1, unacceptable toxicity, or withdrawal of consent to treatment. If clinical progression is suspected, the confirmation of PD with a computed tomography (CT) scan or by magnetic resonance imaging (MRI) per RECIST Version 1.1 will be required. Patients may opt to continue to receive treatment with CO-1686 or erlotinib following radiographic progression as outlined in the National Comprehensive Cancer Network (NCCN) guidelines for treatment of NSCLC with EGFR-TKIs[18] if: a) the patient provides additional consent, b) the investigator feels it is in the patient's best interest, and c) the sponsor provides approval. In general, eligible patients may include those with asymptomatic systemic progression or locally symptomatic progression, such as brain metastases amenable to local treatment, with concomitant asymptomatic systemic progression or continued systemic disease control. Palliative radiotherapy should be discussed prospectively with the sponsor. Patients will undergo serial assessments for anti-tumor efficacy, drug safety, PK, PRO, and biomarkers. Tumor scans will be acquired by the investigative site and evaluated locally for patient treatment decisions. Scans will also be collected and stored with a central vendor and quality control performed; central reading of scans will not be done unless requested by the sponsor. All patients will provide a tumor biopsy (core or fine needle aspiration [FNA]) during screening for determination of EGFR mutation status. For both the Phase 2 and 3 parts, local laboratory testing will be used to determine the presence of an activating EGFR mutation. EGFR mutation

	status will be confirmed by central testing retrospectively. AEs will be collected from the time the first dose of CO-1686 or erlotinib is administered through 28 days after the last dose. Study procedure-related AEs that occur after signing of the Informed Consent Form (ICF) but before administration of CO-1686 or erlotinib will also be captured. Local laboratories will be used for hematology, chemistry and urinalysis. ECGs will be performed and interpreted locally for patient care decisions; however, tracings will be collected centrally for independent evaluation. QOL will be assessed using the EORTC QLQ-C30, EORTC QLQ-LC13, the DLQI, and the EQ-5D instruments.[15-17] Sparse blood sampling for population PK analyses will be conducted in all patients initially randomized and treated with CO-1686. Serial blood sampling for longitudinal quantitative assessment of ctDNA will be conducted in all patients. Tissue and blood samples from both treatment arms will be used to explore biomarkers that may be predictive of response or primary resistance to CO-1686 and/or erlotinib. Following disease progression on CO-1686 or erlotinib, patients can consent to provide an optional additional biopsy before subsequent therapy is initiated. This is a requirement to be eligible for crossover in the Phase 2 part of the study. Upon treatment discontinuation all patients will enter the follow-up phase to monitor for progression every 8 ± 1 weeks (if treatment is discontinued prior to progression), and survival status and subsequent NSCLC treatment approximately every 3 months until death or sponsor decision, whichever comes first.
Study Population	**Inclusion Criteria** All patients must meet all of the following inclusion criteria: 1. Histologically or cytologically confirmed metastatic or unresectable locally advanced/metastatic NSCLC 2. Documented evidence of a tumor with activating EGFR mutations by local testing • Patients with exon 20 insertions are not eligible with the exception of patients with documented evidence of the exon 20 insertion A763_Y764insFQEA in the EGFR gene 3. Have undergone a biopsy or surgical resection of either primary or metastatic tumor tissue within 60 days of the first day of study treatment, Cycle 1 Day 1 (C1D1) and have tissue available to send to sponsor laboratories or are able to undergo a biopsy during screening and provide tissue to sponsor laboratories 4. Measureable disease according to RECIST Version 1.1 5. Life expectancy of at least 3 months 6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 7. Age ≥ 18 years (in certain territories, the minimum age requirement may be higher e.g., age ≥ 20 years in Japan and Taiwan) 8. Adequate hematological and biological function, confirmed by the following laboratory values: • <u>Bone Marrow Function</u> o Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L

	○ Platelets > 100.0 × 10^9/L ○ Hemoglobin ≥ 9 g/dL (or 5.6 mmol/L) • Hepatic Function ○ Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 × upper limit of normal (ULN); if liver metastases, ≤ 5 × ULN ○ Bilirubin ≤ 2 × ULN (Patients with documented Gilbert's syndrome and conjugated bilirubin within normal range may be allowed into the study. In this event, it will be documented that the patient was eligible based on conjugated bilirubin levels) • Renal Function ○ Serum creatinine ≤ 1.5 × ULN • Electrolytes ○ Potassium and magnesium within normal range, patients may receive supplements to meet this requirement 9. Written informed consent on an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved ICF prior to any study-specific evaluation
	Exclusion Criteria Any of the following criteria will exclude patients from study participation: 1. Documented evidence of an exon 20 insertion activating mutation other than A763_Y764insFQEA in the EGFR gene 2. Prior treatment with cytotoxic chemotherapy for advanced NSCLC; neoadjuvant/adjuvant chemotherapy is permitted if at least 6 months has elapsed between the end of chemotherapy and randomization 3. Active second malignancy; i.e., patient known to have potentially fatal cancer present for which he/she may be (but not necessarily) currently receiving treatment • Patients with a history of malignancy that has been completely treated and currently with no evidence of that cancer, are permitted to enroll in the trial provided all chemotherapy was completed > 6 months prior and/or bone marrow transplant > 2 years prior to first day of study treatment, C1D1 4. Known pre-existing interstitial lung disease (ILD) 5. Brain metastases 6. Treatment with prohibited medications (e.g., concurrent anticancer therapy including other chemotherapy, radiation, hormonal treatment [except corticosteroids and megesterol acetate], or immunotherapy) ≤ 14 days prior to first day of study treatment, C1D1 7. Patients who are currently receiving treatment with any medications that have the potential to prolong the QT interval if that treatment cannot be either discontinued or switched to a different medication (not known to affect QT interval) prior to C1D1 • See http://crediblemeds.org/ for a current list of QT-prolonging medications 8. Prior treatment with EGFR-TKIs (e.g., erlotinib, gefitinib, neratinib, afatinib, AZD9291, or dacomitinib), CO-1686 or other drugs that target mutant EGFR

	9. Any of the following cardiac abnormalities or history: • Clinically significant abnormal 12-lead ECG, QT interval corrected using Fridericia's method (QT_CF) > 450 ms • Inability to measure QT interval on ECG • Personal or family history of long QT syndrome • Implantable pacemaker or implantable cardioverter defibrillator • Resting bradycardia < 55 beats/min 10. Non-study related surgical procedures ≤ 7 days prior to C1D1. In all cases, the patient must be sufficiently recovered and stable before treatment administration. 11. Females who are pregnant or breastfeeding 12. Refusal to use adequate contraception for fertile patients (females and males) during study treatment and for 12 weeks after the last dose of CO-1686 and 2 weeks after the last dose of erlotinib 13. Presence of any serious or unstable concomitant systemic disorder incompatible with the clinical study (e.g., substance abuse, uncontrolled intercurrent illness including uncontrolled diabetes, active infection, arterial thrombosis, and symptomatic pulmonary embolism) 14. Any other reason the investigator considers the patient should not participate in the study
Study Treatment	CO-1686 will be administered to patients as oral tablets on a BID basis. Patients will be instructed to take CO-1686 at 500 mg BID with a meal or within 30 minutes after a meal. Erlotinib will be taken QD at 150 mg, on an empty stomach; i.e., at least 1 hour before or 2 hours after the ingestion of food.[19]
Randomization	Following confirmation of patient eligibility by the sponsor, patients will be centrally randomized in a 1:1 ratio to receive oral CO-1686 or erlotinib. Patients will be stratified according to sensitizing EGFR mutation present (del19, L858R, or other) and territory of residence at time of randomization (Asia vs. non-Asia). Study treatment (C1D1) should be initiated no later than 3 days from date of randomization.
Dose-modification Criteria	*CO-1686* No dose escalation above the starting dose is allowed. Two dose reduction steps are allowed for each patient. The dose reductions are from 500 mg BID (the starting dose) to 375 mg BID, then 250 mg BID. The dose of CO-1686 should not be reduced below 250 mg BID without prior sponsor approval. For National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03[20] Grade 3 or 4 hematologic and non-hematologic toxicities (except for nausea/vomiting, alopecia, QTc prolongation and hyperglycemia), the dose should be initially reduced to 375 mg BID and, if persistent, to 250 mg BID for subsequent doses if the investigator and sponsor do not believe treatment discontinuation is required. Re-escalation of dose after resolution of AEs must be discussed and approved by sponsor prospectively. If QT_C prolongation of CTCAE Version 4.03 Grade 3 is observed, CO-1686 will be held until the event has improved to Grade 1. CO-1686 can then be re-started at a reduced dose after sponsor approval. After 2 dose reductions, if CTCAE Grade 3 QT_C prolongation recurs, then CO-1686 will be discontinued unless agreed with the

	sponsor that additional dose reduction may be considered. If QT_C prolongation changes of CTCAE Grade 4 are observed at any time, CO-1686 will be discontinued permanently. If a patient experiences hyperglycemia, dose management should be as outlined in protocol Section 7.4.1. *Erlotinib* Dose modifications for erlotinib are allowed in accordance with its prescribing information. Erlotinib will be withheld for: • Acute onset of new or progressive unexplained pulmonary symptoms such as dyspnea, cough, and fever pending diagnostic evaluation for possible ILD • CTCAE Grade 3 to 4 renal toxicity • Total bilirubin levels > 3 x ULN or transaminases > 5 x ULN in patients without pre-existing hepatic impairment • Total bilirubin > 2 x ULN or transaminases > 3 x ULN in patients with pre-existing hepatic impairment or biliary obstruction • Persistent severe diarrhea not responsive to medical management • Acute/worsening ocular disorders such as eye pain • Severe rash not responsive to medical management • Keratitis of Grade 3 to 4 or for Grade 2 lasting more than 2 weeks Following interruption of erlotinib treatment for toxicity, once the event has resolved to baseline or Grade ≤ 1, erlotinib can be restarted with a 50 mg decrease with prospective sponsor approval. Erlotinib will be discontinued if: • ILD is confirmed • Abnormal liver tests meeting the criteria for drug withhold as defined above do not improve to Grade 1 or baseline levels within 3 weeks • Patient develops gastrointestinal perforation • Patient develops severe bullous, blistering or exfoliating conditions • Patient develops corneal perforation or severe ulceration • A toxicity requiring erlotinib to be withheld does not improve or recurs on initiation of erlotinib
Concomitant Medications	Supportive care (e.g., antiemetics, analgesics) may be used at the investigator's discretion and in accordance with institutional procedures.
Withdrawal Criteria	A patient must be discontinued from protocol-prescribed therapy if any of the following apply: • Consent withdrawal at the patient's own request or at the request of their legally authorized representative

	• Radiographically documented disease progression of patient's underlying disease, except as described in protocol Section 5.1.2. If clinical progression is diagnosed then confirmation with a CT scan or by MRI will be required before patient withdrawal. • Any event, adverse or otherwise, that, in the opinion of the investigator, would pose an unacceptable safety risk to the patient • An intercurrent illness that, in the opinion of the investigator, would affect assessments of the clinical status to a significant degree and requires discontinuation of therapy • A positive pregnancy test at any time during the study • Noncompliance as described in protocol Section 7.7 • Investigator decision After stopping protocol-specified treatment (initial study treatment or crossover treatment, whichever comes last), all patients will remain in the study and will be followed for safety (through 28 days after last dose), subsequent NSCLC therapies, and survival status (every 3 months [± 1 week]) until death or sponsor decision, whichever comes first. Patients who discontinue treatment without progression should continue to be scanned every 8 ± 1 weeks per protocol until radiographic disease progression occurs.
Efficacy Assessments	Efficacy measures will include tumor assessments, preferably by CT scans of the chest and abdomen with appropriate slice thickness per RECIST Version 1.1; scans of the pelvis (CT or MRI) will be required if there is prior evidence of local disease or if clinically indicated (symptomatic patients); other studies (MRI and X-ray) may be performed if required. Brain imaging (CT/MRI) is required at baseline. Patients with brain lesions known or detected at baseline are not eligible for the study. Tumor assessments will be performed at screening and every 8 ± 1 weeks thereafter (Day 1 of Cycles 3, 5, 7, etc.), including at the End-of-Treatment Visit, if radiographic disease progression has not been documented previously. Patients who discontinue treatment without progression should continue to be scanned every 8 ± 1 weeks per protocol until radiographic disease progression occurs. In the Phase 2 part only, during the crossover portion of the study, scans will be collected at the frequency noted in protocol Section 9.3. An MRI may be used in place of a CT at end-of-treatment scan if required per local authorities.
Safety Assessments	Safety measures will include: • AEs • Hematology, including reticulocyte count, clinical chemistry including fasting glucose, hemoglobin A1c (HbA1c), and urinalysis • 12-lead ECGs • Physical examination • Vital signs, body weight and height • Concomitant medications/procedures

	• ECOG performance status Where applicable, AEs will be classified according to the NCI CTCAE Version 4.03.[20]
Biomarker Assessments	• In addition to local laboratory testing required for confirmation of eligibility, EGFR mutational status will be assessed in matching blood and formalin-fixed paraffin-embedded (FFPE) tumor tissue collected at screening from each patient by sponsor and/or central laboratory. Tumor tissue from the primary tumor, or an accessible metastatic lesion, will be obtained within 60 days prior to dosing. The corresponding blood specimen will be obtained immediately prior to tumor specimen collection where possible. Dates of tumor samples will be collected. EGFR-mutational status on collected tissue and blood will be assessed by the sponsor. • Blood will be collected for detection and quantification of mutant EGFR from plasma. Patients will have blood collected during screening, at every cycle Day 1 visit, C1D15 and at disease progression. • Following disease progression on randomized treatment, patients who provide additional consent will undergo tumor biopsy before subsequent-line therapy is initiated. • In the Phase 2 part only, in order to be eligible for the crossover portion of the study, erlotinib-treated patients must have an additional biopsy upon progression and within 35 days prior to dosing with CO-1686 to confirm T790M+ status and meet specific eligibility requirements. • Blood and tissues specimens collected from patients will be used to investigate the genetic and transcriptional changes associated with response and resistance to erlotinib and CO-1686, for example targeted exon sequencing of 'clinically significant' cancer genes using next-generation sequencing technology. Extracted genomic deoxyribonucleic acid (DNA) from blood may be compared to tumor DNA so that genetic alterations unique to the tumor that may modulate response or resistance to EGFR-targeted therapy can be unambiguously identified. • For patients who provide additional consent and are randomized to CO-1686, genomic DNA will be extracted from a blood sample in order to detect genetic polymorphisms in cytochrome P450 (CYP) isozymes and to explore the possible correlation between CYP polymorphism and CO-1686 drug exposure. The extracted genomic DNA from blood may additionally be compared to tumor DNA so that molecular alterations unique to the tumor that may modulate response or resistance to EGFR-targeted therapy can be unambiguously identified.
Patient Reported Outcome Assessments	PRO will be measured using the EORTC QLQ-C30 and LC13,[15] the DLQI,[16] and the EQ-5D,[17] which will be administered at screening, prior to dosing on C1D1 then every 8 ± 1 weeks for 6 months (Day 1 of Cycles 3, 5, 7). After Cycle 7 Day 1 visit, questionnaires will be collected every 12 ± 1 weeks (Day 1 of Cycles 10, 13, 16, etc.) and at end-of-treatment**.** For patients who crossover to CO-1686 following progression on erlotinib, baseline PRO will be collected prior to dosing with CO-1686, then at the frequency described above with crossover cycles (XO-Cs) following all on-study cycle visit schedules.

Statistical Procedures	**Analysis Populations** • Intent-to-treat (ITT) population – all randomized patients; the primary efficacy analysis of the Phase 3 part will be performed using the ITT population • Tumor evaluable population – all patients who received at least 1 dose of first-line CO-1686 or erlotinib, have measureable tumor lesions at baseline, and have at least 1 post-baseline tumor assessment • Safety population - all patients who have received at least 1 dose of CO-1686 or erlotinib **Sample Size Justification** Up to 1,200 patients will be randomized in a 1:1 ratio to receive treatment with CO-1686 or erlotinib. The Phase 2 part will randomize approximately 200 patients and the Phase 3 part will randomize up to 1,000 patients. The primary objective of this study is to estimate the relative improvement in PFS for CO-1686 as compared with erlotinib. The median PFS for erlotinib in this patient population is expected to be approximately 10 months. If CO-1686 has a 13-month median PFS, then the hazard ratio (HR) comparing CO-1686 with erlotinib will be approximately 0.80. For the Phase 3 part of the study, a total of 640 PFS events will provide approximately 80% power to detect a HR of 0.80 at a 0.025 (1-sided) significance level for the comparison of CO-1686 versus erlotinib. **Efficacy Analysis** Kaplan-Meier methodology will be used to summarize time-to-event variables. The stratified logrank and HR will be used for comparing the PFS distributions among the CO-1686 and erlotinib treated patients. The ORR will be summarized with frequencies and percentages. **Safety Analysis** Data from all patients who receive 1 or more doses of CO-1686 or erlotinib will be included in the safety analyses. AEs, clinical laboratory information, vital signs, ECOG performance status, body weight, and concomitant medications/procedures will be tabulated and summarized. **Interim Analysis** A data monitoring committee (DMC) will periodically review efficacy and safety data to ensure that a positive risk/benefit ratio is maintained throughout the study. For the unblinded Phase 2 part, the DMC will consist of sponsor designated personnel and the primary investigators and will review safety approximately every 3 months. The first DMC meeting will take place once 25 patients have completed 2 cycles on protocol-specified treatment. For the Phase 3 part, the sponsor will remain blinded to efficacy and safety results aggregated by randomized treatment group and an independent data monitoring committee (IDMC) will review safety data on a quarterly basis for the first year, and meet at least twice a year thereafter. In addition to the aforementioned safety analyses, the IDMC will be convened for up to 3 formal interim efficacy analyses. These analyses will be triggered by randomization of the 600th, 700th, and 800th patients into the Phase 3 part. The formal interim efficacy analyses are based on a Bayesian adaptive design that combines the data from the Phase 2 and Phase 3 parts. If the combined data indicate a high probability (> 99%) of success for the Phase 3 part of the study, then

	enrollment into the Phase 3 part of the study may be stopped prior to enrollment of 1,000 patients. The study will end when at least 70% of the randomized patients in the Phase 3 part have experienced a PFS event. If timing of interim efficacy and safety analyses fall within 2 months of each other, then the sponsor may request to combine such IDMC reviews.

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AAG	alpha-1 acid protein
AE	adverse event
ALT	alanine transaminase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
AST	aspartate transaminase
AUC	area under the curve
$AUC_{0–24}$	area under the curve from time zero to 24 hours
BID	twice daily
BUN	blood urea nitrogen
C1D1	Cycle 1 Day 1
CFR	Code of Federal Regulations
CI	confidence interval
Clovis	Clovis Oncology, Inc.
CO-1686 FB	free base form of CO-1686
CO-1686 HBr	hydrobromide salt formulation CO-1686
CO_2	Bicarbonate
C_{12h}	concentration 12 hours post dose
C_{max}	maximum concentration
CR	complete response
CRO	contract research organization
CT	computed tomography
ctDNA	circulating tumor DNA
CTCAE	Common Terminology Criteria for Adverse Events (Version 4.03)
CYP	cytochrome P450
DCR	disease control rate
DLQI	Dermatology Life Quality Index
DLT	dose-limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor

EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire
EORTC QLQ-LC13	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer module
EURTAC	European Tarceva® versus Chemotherapy Study
FB	Free base
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FNA	fine needle aspiration
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practice
GRAS	generally regarded as safe
HbA1c	hemoglobin A1c
HBr	hydrobromide
HCP	health care practitioner
HIPAA	Health Information Portability and Accountability Act
HR	hazard ratio
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDMC	independent data monitoring committee
IEC	Independent Ethics Committee
ILD	interstitial lung disease
invPFS	progression-free survival determined by investigator review
iPASS	Iressa™ Pan-Asian Study
IRB	Institutional Review Board
irrPFS	independent radiographic review of PFS
ITT	intent-to-treat
IV	intravenous
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	not evaluable
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease

PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PO	by mouth
POPPK	population pharmacokinetics
PR	partial response
PRO	patient-reported outcomes
QD	once daily
QOL	quality of life
QT_CF	QT interval corrected using Fridericia's method
RECIST	Response Evaluation Criteria in Solid Tumors, Version 1.1
SAE	serious adverse event
SAS	statistical analysis software
SLD	sum of longest diameters of target lesions
SUSAR	suspected unexpected serious adverse reaction
$T_{1/2}$	elimination half-life
T790M	EGFR mutation in exon 20, gatekeeper mutation
T790M+	T790M positive
TID	3 times daily
TKI	tyrosine kinase inhibitor
T_{max}	time to maximum concentration
ULN	upper limit of normal
WBC	white blood cell
WT	wild-type
XO-C	crossover cycle

3 INTRODUCTION

CO-1686 Clinical Development Program Update

In mid-2015, Clovis submitted a New Drug Application for the use of CO-1686 in patients with T790M-positive NSCLC. In June 2016, the FDA issued a Complete Response Letter to Clovis stating that more data are required to approve CO-1686 for use outside of a clinical trial. Based on this outcome, Clovis decided to discontinue development of CO-1686 for NSCLC. Patients will be informed of this change in the development plans in an update to the informed consent form for this study. Those patients who continue to derive clinical benefit from study treatment, will be allowed to continue on study at the discretion of the Principal Investigator in an extension phase.

Extension Phase

The purpose of this protocol amendment is to add a new Extension Phase to allow patients to continue on study but to avoid unnecessary collection of data that will no longer be analyzed or required for regulatory purposes, whilst maintaining an appropriate level of safety monitoring. A new schedule of assessments for the Extension Phase as well as a complete description of procedures is provided in Appendix D. This schedule replaces all schedules of assessments in Section 9 and should be followed for all patients.

An important change of the Extension phase is the removal of the option for patients to crossover to CO-1686 following radiographic progression on erlotinib. The decision to remove the crossover option to CO-1686 was based on the recommendation of the DMC, which oversees the risk/benefit aspects of the study. Patients and their physicians are directed to seek alternative treatments, which can fulfill this need.

For patients who wish to continue CO-1686 or erlotinib treatment post progression, it is important that a full exploration of alternative treatment options between patients and their treating physicians takes place.

In addition, this amendment also introduces the availability of NAT2 testing for patients, an indirect indicator of the likelihood of developing hyperglycaemia and QTc prolongation. The availability and disclosure of this information to the patient's treating physician will not affect the monitoring and associated treatment guidelines for these adverse events.

Investigators and their staff are directed to the current Investigator's Brochure for the most current efficacy and safety data, in which integrated summaries of the latest available data can be found and supersedes all safety and efficacy data in this protocol

3.1 Mutant EGFR Non-small Cell Lung Cancer

Despite years of research and prevention strategies, lung cancer continues to be the most common cause of cancer-related deaths worldwide,[21] with a 5-year survival rate of less than 10% in patients with advanced disease.[22]

Cytotoxic chemotherapy has been the mainstay of treatment for patients with non-small cell lung cancer (NSCLC), however survival rates remain low and toxicity is significant. Recent

breakthroughs in NSCLC treatment have been a result of molecular characterization of NSCLC and development of molecularly targeted agents demonstrate superiority to chemotherapy in patients harboring tumors with the targeted genetic mutation(s).

Activating epidermal growth factor receptor (EGFR) mutations are key drivers of NSCLC malignancy in 10% to 15% of patients of European descent and approximately 30% of patients of Asian descent.[1] Treatment of such patients with EGFR inhibitors is now standard of care, following demonstration of superiority over cytotoxic chemotherapy in Phase 3 studies of erlotinib, gefitinib and afatinib.[2,23-26] In the Iressa™ Pan-Asia Study (iPASS) trial, treatment with gefitinib was compared to treatment with carboplatin/paclitaxel in previously untreated NSCLC patients. In EGFR-mutation-positive patients, the response rate was significantly higher with gefitinib treatment (71.2%) than with chemotherapy (47.3%).[2] Furthermore, EGFR-mutation-positive patients experienced a significantly longer progression-free survival (PFS) of 9.5 months compared to 6.3 months for those on chemotherapy.[27] A second Phase 3 randomized trial, the European Tarceva® (erlotinib) versus chemotherapy (EURTAC) study, compared treatment with erlotinib to chemotherapy in previously untreated patients with EGFR-mutation-positive NSCLC. Data from this study show that patients demonstrate a response rate of 58% in the erlotinib arm compared to 15% in the chemotherapy arm ($p < 0.0001$). PFS was 9.7 months in the erlotinib arm versus 5.2 months in the chemotherapy arm (hazard ratio [HR] = 0.37; $p < 0.0001$).[28] Two recent large randomized Phase 3 trials comparing afatinib with standard chemotherapy in previously untreated patients with EGFR mutant NSCLC, gave response rates of 56% and 67% on afatinib versus 23% on chemotherapy. PFS was 11.0 and 13.6 months in the afatinib arms versus 5.6 and 6.9 months in the chemotherapy arms.[4,29] These data demonstrate that gefitinib, erlotinib, and afatinib improve response rates and PFS compared to chemotherapy.

While the toxicity profile is also improved with first-generation tyrosine kinase inhibitors (TKIs) compared to chemotherapy, significant toxicities do occur. Toxicity associated with erlotinib, gefitinib and afatinib includes skin rash and diarrhea related to inhibition of the wild-type (WT, normal) EGFR in skin and intestine, respectively.[5-7]

Sequist et al analyzed serial biopsies from EGFR-mutation-positive NSCLC patients who progressed on TKIs.[30] Through this research, Sequist demonstrated that acquired resistance occurs through a number of different mechanisms, while the activating mutation is maintained. In that analysis, the most common cause of clinical progression (in 50% of patients) was found to be a second site EGFR mutation in exon 20 called T790M (the "gatekeeper" mutation), which prevents drug from binding to the receptor.[3,8,9,30] Resistance was sometimes associated with amplification of the EGFR gene as well. Some patients developed amplification of another gene that drives tumor growth (MET proto-oncogene [MET] gene amplification). Still others showed mutations in the phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (PIK3CA) gene. Interestingly, a few patients had tumors that transitioned to a small cell lung cancer, or to a more aggressive mesenchymal cell morphology.[30] More recently, Yu et al evaluated tumor biopsies from 155 patients who had developed acquired resistance to gefitinib or erlotinib. Of those, 98 samples (63%) showed EGFR T790M as the driver of resistance.[10] Furthermore, a small group of mutant EGFR NSCLC patients (~2% to 3%) will exhibit T790M mutations in tumor at baseline (so-called "*de novo*" T790M disease) and these patients are known to have very poor outcomes on standard TKI therapy.[11,12] Some of these patients may

have germline T790M mutations, and they typically develop clinical lung cancer only when a classical "activating "mutation (such as L858R or del19) occurs as a second hit.[13]

CO-1686 is a novel, potent, small molecule irreversible TKI that selectively targets mutant forms of the EGFR.[31] In nonclinical models, CO-1686 is active against the common initial activating mutations of CO-1686 and against the T790M resistance mutation described. In addition, it does not inhibit WT EGFR. In an ongoing study of second and later line disease (Study CO-1686-008), durable responses are observed in patients with heavily pretreated EGFR mutant NSCLC. Therefore, the rationale exists to study CO-1686 in the first-line setting where it may be active without the toxicities associated with inhibition of WT-EGFR.

3.1 Nonclinical Overview

CO-1686 is a novel, potent, small molecule irreversible TKI that selectively targets mutant forms of the EGFR. Clovis Oncology, Inc. (Clovis), is developing CO-1686 as a therapeutic agent to be administered orally to patients with mutant EGFR NSCLC. CO-1686 inhibits the EGFR gatekeeper mutation (T790M) which is associated with clinical resistance to erlotinib and gefitinib as well as the common EGFR-activating mutations (L858R, del19) and has minimal inhibitory activity towards the WT-EGFR at clinically relevant doses.

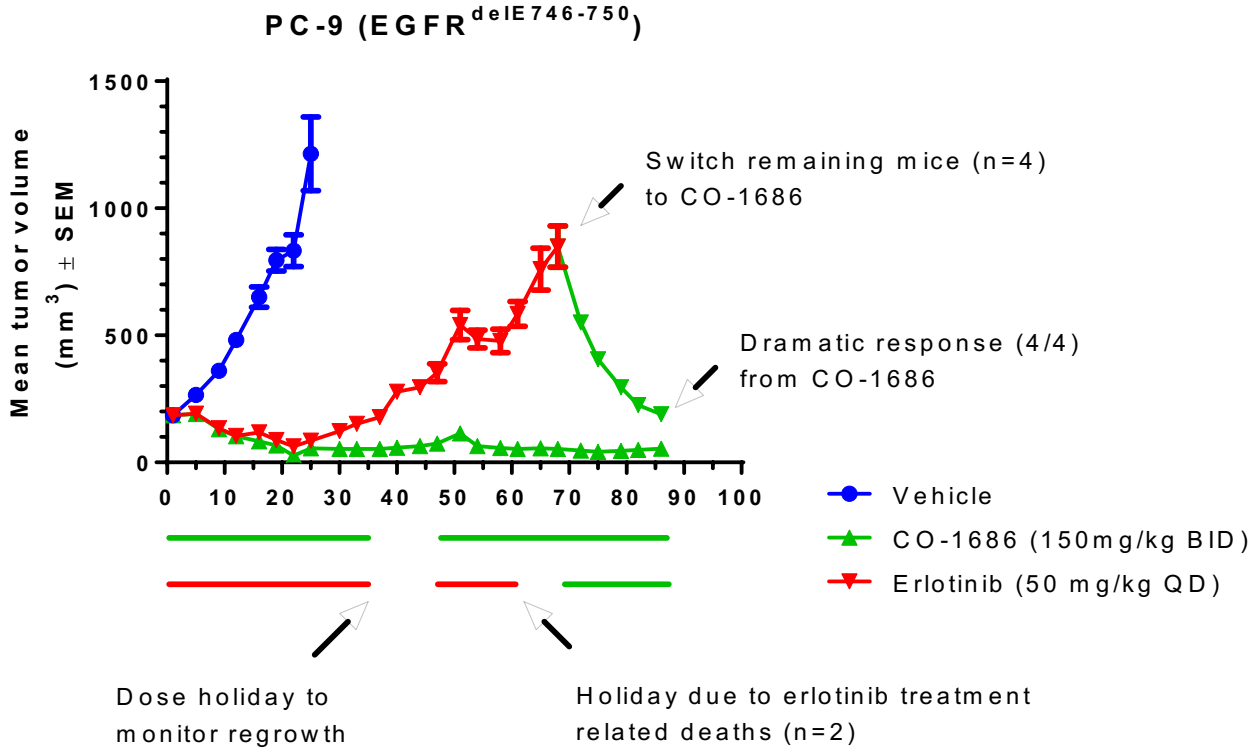
CO-1686 has been evaluated as a free base formulation (CO-1686 free base) and as a hydrobromide salt formulation (CO-1686 HBr). The pharmacologically active moiety, irrespective of formulation, is CO-1686.

Pharmacology

CO-1686 exhibits potent anti-tumor activity and EGFR pathway inhibition as a single agent in HCC827 and PC9 cell lines expressing the $EGFR^{del19}$ mutation.[31]

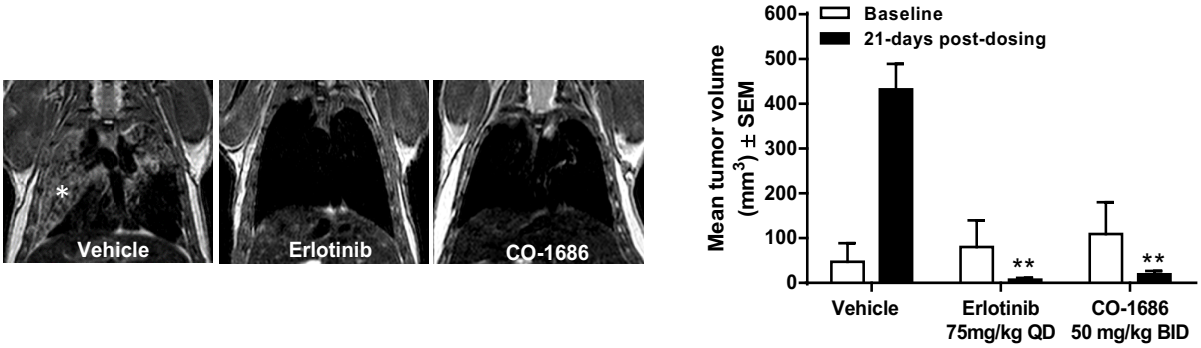
The efficacy of CO-1686 was evaluated in 2 different first-line subcutaneous xenograft models, HCC827 ($EGFR^{del19}$) and PC9 ($EGFR^{del19}$). In the HCC827 model dosing of CO-1686 resulted in a significant reduction in tumor volumes comparable to that observed with erlotinib. In the first-line PC-9 ($EGFR^{del19}$) subcutaneous xenograft model significant reductions in tumor volume were observed in both erlotinib and CO-1686 treated mice as compared to the vehicle group (Figure 3-1), with CO-1686 providing a statistically significant reduction in tumor volume as compared to erlotinib following prolonged dosing. From approximately Day 25 onward the tumors in mice treated with erlotinib continued to increase in size through the expansion of a T790M positive (T790M+) subclone likely present at a low frequency in the original PC9 cell line.[32] A cohort of mice with large (~700mm^3) erlotinib resistant tumors were switched to CO-1686 dosing. In all of the mice treated with CO-1686 (n = 4) the tumors significantly decreased in size. These data suggest that irreversible inhibitors such as CO-1686 may delay or prevent the emergence of resistance, resulting in prolonged time to disease progression as compared to erlotinib, gefitinib, and afatinib.

Figure 3-1: CO-1686 Generates Potent Anti-tumor Response in First-line PC-9 ($EGFR^{del19}$) Xenograft Model



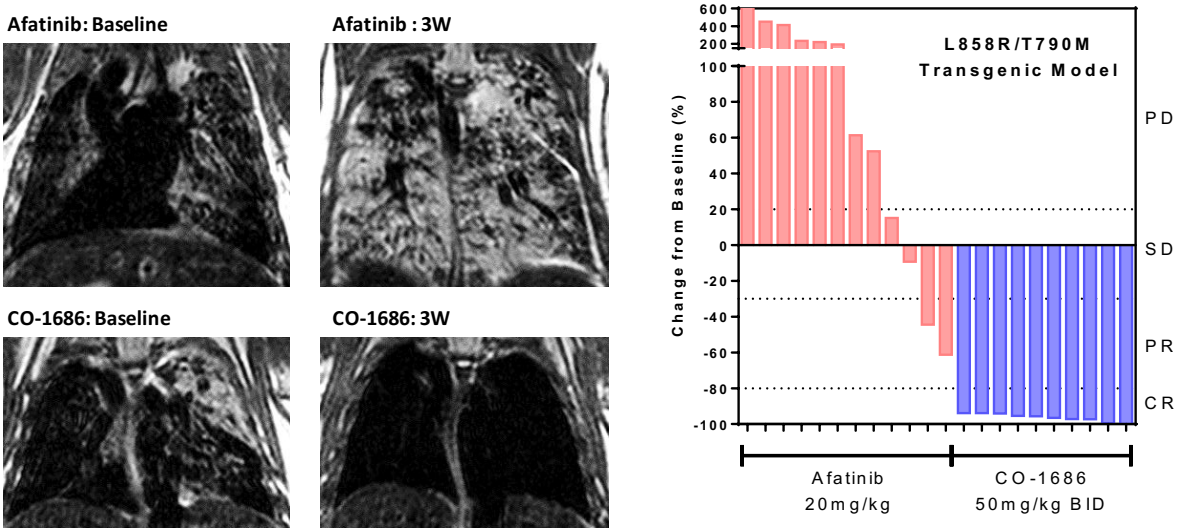
There are no commercially available tumor cell lines that express the first-line $EGFR^{L858R}$ mutation, thus an $EGFR^{L858R}$ transgenic model was used to assess the activity of CO-1686 in tumors expressing this common activating mutation. In the $EGFR^{L858R}$ transgenic model, CO-1686 administration resulted in potent and comparable anti-tumor activity to that of erlotinib (Figure 3-2). Thus, CO-1686 shows potent single-agent activity in xenograft models expressing both common first-line EGFR mutations.

Figure 3-2: CO-1686 Generates more Durable Anti-tumor Response than Erlotinib in First-line EGFR^{L858R} Transgenic Model



In an estimated 50% to 60% of patients the resistance to current EGFR-TKIs is driven by a secondary T790M mutation in EGFR, and a clinically effective T790M inhibitor may delay the emergence of resistance and increase the time to disease progression as compared to erlotinib, gefitinib, and afatinib. CO-1686 demonstrated potent *in vitro* and *in vivo* pathway inhibition and anti-tumor activity in NCI-H1975 (EGFR$^{L858R/T790M}$) cells and xenograft models. Potent activity was also observed by administration of CO-1686 as a single agent in the LUM1868 (EGFR$^{L858R/T790M}$) primary subcutaneous xenograft model. In addition, the efficacy of CO-1686 was examined in an EGFR$^{L858R/T790M}$ transgenic model and compared with that of afatinib. Complete responses (CRs) were observed in all mice treated with CO-1686 (Figure 3-3). Taken together, these data suggest it may take longer to acquire T790M-mediated resistance to CO-1686 as compared to first generation TKIs, such that PFS with CO-1686 would be superior to erlotinib, gefitinib, and afatinib.

Figure 3-3: CO-1686 Generates Complete Responses in L858R/T790M Transgenic Model



Weaver Lab, NCI

Metabolism

In human liver microsomes, CO-1686 was slowly metabolized, with cytochrome P450 (CYP) 2C8 playing a role, and CYP2D6 playing a minor role at most. There is no evidence to suggest the involvement of the polymorphically-expressed CYP2C9 and CYP2C19 in CO-1686 metabolism, implying a low potential for ethnic sensitivity variability in humans. CO-1686 is a substrate and an inhibitor of P-glycoprotein (P-gp) and caution should be exercised when CO-1686 is co-administered with P-gp inhibitors and inducers (see Section 8.1.4. for further information). Caution should also be exercised in patients receiving oral CO-1686 and requiring concomitant medication with warfarin (Coumadin®), nonsteroidal anti-inflammatory drugs (NSAIDs), or clopidogrel, as CO-1686 moderately inhibited CYP2C8, CYP2C9 and CYP2C19 activities *in vitro.*

Safety Pharmacology and Toxicology

Safety pharmacology and toxicology studies were performed in rats and dogs with CO-1686 HBr.

Primary indices of toxicity in rats included dose-dependent clinical signs (thinning haircoat in females, squinting, pale ears or body and hunched posture), loss in body weight and decreased body weight gain and food consumption. Increased neutrophil count, decreased white blood cell (WBC) count, lymphocyte count and red blood cell parameters were also noteworthy. Squinting was observed in high dose rats administered CO-1686 HBr and was associated with atrophy of meibomian gland in the eyelid; both effects were reversible. The correlate of this finding in humans is dry eye. Other microscopic findings after 28 days of repeated dosing in rats included minimal to moderate atrophy of other glands (Harderian gland, mammary gland and prostate). Pathological findings were minor glandular atrophy in all 4 tissues which was reversible and principally occurred in the high dose group. Only minor effects were observed with CO-1686 HBr on hematopoietic tissue.

Primary indices of toxicity in the dog included dose-related clinical signs which included abnormal feces (liquid and/or non-formed feces), vomiting and redness of gingiva and lips. These observations were not considered adverse due to the overall good health of the animals. All clinical observations were reversible, except for non-formed feces. The redness of gingiva or lips noted had no microscopic correlation at total exposures of area under the curve (AUC) of up to 23,100 ng·hr/mL.

No evidence of elevated serum glucose levels were observed in the rat and dog studies. There were no CO-1686-related cardiac safety or neurobehavioral findings from the good laboratory practice (GLP) repeat-dose toxicity studies. CO-1686 did not have any genotoxic activity in 2 *in vitro* assays, and was not phototoxic when evaluated in a phototoxicity study with Long Evans pigmented rats.

Please refer to the Investigator's Brochure for detailed information on the nonclinical program.

3.2 Clinical Experience with CO-1686

CO-1686 has been evaluated in Study CO-1686-008, an ongoing first-in-human Phase 1/2 study in patients with advanced NSCLC and 1 completed Phase 1 study in healthy volunteers (CO-1686-016).

3.2.1 Safety

Study CO-1686-008

CO-1686-008 is a 2-part, open-label, safety, pharmacokinetic (PK), and preliminary efficacy study of CO-1686 in patients with advanced/metastatic NSCLC. As of 04 June 2014, 148 patients with advanced/metastatic NSCLC have received at least 1 dose of CO-1686. In the initial stage of the study, 57 patients were treated with CO-1686 administered as free base capsules at doses ranging from 150 mg up to 1800 mg daily. Subsequently, CO-1686 HBr tablets were introduced into the study to be used in the later dose escalation cohorts. Ninety-one patients have been treated with CO-1686 administered as HBr tablets at doses of 500 mg twice daily (BID) (n = 18), 625 mg BID (n = 17), 750 mg BID (n = 50) and 1000 mg BID (n = 6). At the time of this summary, preliminary safety data are available in the clinical database for 148 patients.

Dose-limiting Toxicities (DLTs): Enrollment of patients to the dose escalation phase was completed in February 2014 with a DLT rate of < 33% at all evaluated doses. The DLT evaluable population included all patients who have completed Cycle 1 and who were enrolled while the dose escalation part of the study was ongoing. The most frequently reported DLT was hyperglycemia/glucose tolerance impaired which occurred at a similar frequency (10% to 20%) across all CO-1686 HBr dose levels (500 mg BID, 625 mg BID, 750 mg BID, 1000 mg BID). Hyperglycemia has been effectively managed with the addition of anti-hyperglycemic therapy and/or dose reductions. Guidance for the management of hyperglycemia associated with CO-1686 treatment is provided in Section 7.4.1.

Serious Adverse Events (SAEs): A total of 43 patients experienced at least 1 SAE and 17 patients reported an SAE assessed as related to study drug. Treatment-related SAEs are summarized in Table 3-1. There were 11 deaths while on study or within 28 days after last dose. Eight deaths were due to progression of NSCLC, 1 due to pneumonia, 1 due to pulmonary embolism, and 1 of unknown cause, with all assessed as not related to study drug.

Table 3-1: Treatment-related SAEs Reported in any Patient in Study CO-1686-008

Daily Dose	< 1800 mg (N = 38)	1800 mg (N = 19)	1000 mg (N = 18)	1250 mg (N = 17)	1500 mg (N = 50)	2000 mg (N = 6)	Overall (N = 148)
Formulation	FB	FB	HBr	HBr	HBr	HBr	
Frequency	Various[a]	900 mg BID	500 mg BID	625 mg BID	750 mg BID	1000 mg BID	
Overall	4 (10.5%)	1 (5.3%)	4 (22.2%)	3 (17.6%)	4 (8.0%)	1 (16.7%)	17 (11.5%)
Cardiac Disorders							
Pericarditis	1 (2.6%)	0	0	0	0	0	1 (0.7%)
Gastrointestinal Disorders							
Diarrhea	1 (2.6%)	1 (5.3%)	0	0	0	0	2 (1.4%)
Nausea	1 (2.6%)	0	1 (5.6%)	0	1 (2.0%)	0	3 (2.0%)
Pancreatitis	0	0	1 (5.6%)	0	0	0	1 (0.7%)
Vomiting	2 (5.3%)	0	1 (5.6%)	0	1 (2.0%)	0	4 (2.7%)
Infections and Infestations							
Gastroenteritis	0	0	0	0	1 (2.0%)	0	1 (0.7%)
Investigations							
ECG QT prolonged	0	0	0	1 (5.9%)	1 (2.0%)	0	2 (1.4%)
ECG T wave inversion	0	0	0	0	1 (2.0%)	0	1 (0.7%)
Transaminases increased	0	1 (5.3%)	0	0	0	0	1 (0.7%)
Metabolism and Nutrition Disorders							
Decreased appetite	0	1 (5.3%)	0	0	0	0	1 (0.7%)
Combined terms of hyperglycemia	1 (2.6%)	0	4 (22.2%)	1 (5.9%)	2 (4.0%)	1 (16.7%)	9 (6.1%)
Hypoglycemia	1 (2.6%)	0	0	0	0	0	1 (0.7%)
Hypokalemia	0	0	0	1 (5.9%)	0	0	1 (0.7%)
Respiratory, Thoracic and Mediastinal Disorders							
Pneumonitis	0	0	0	1 (5.9%)	0	0	1 (0.7%)

Abbreviations: FB = free base

[a] 150 mg to 900 mg daily (QD), 100 mg to 600 mg twice daily (BID), 400 mg 3 times a day (TID)

Treatment-related Adverse Events (AEs): Treatment-related AEs reported in at least 5% of patients summarized in Table 3-2.

The most frequently reported treatment-related AEs (all grades) were nausea (28.4%), and hyperglycemia/glucose tolerance impaired (33.1%). The majority of AEs are mild or moderate. The most frequently reported Grade 3 or higher AE, occurring in 18.5% of patients overall, was hyperglycemia/glucose tolerance impaired.

As expected due to CO-1686 selectivity for mutant EGFR, dose related WT-driven rash and diarrhea has not been observed. All reported events of diarrhea were either Grade 1 or Grade 2.

The most common skin reaction reported in patients treated with EGFR-TKIs is a follicular acneiform eruption. In Study CO-1686-008, rash, irrespective of causality, was reported infrequently (overall 7 patients; 5.4%) and events were mild. Only 1 event of dermatitis acneiform and 1 event of follicular rash have been reported.

There has been 1 AE and 1 SAE of pneumonitis. Both events were assessed as related to CO-1686. Both cases resolved when CO-1686 treatment was stopped.

Electrocardiograms (ECGs): ECG results are available for 122 patients. CO-1686 causes an increase in the QTc interval of the ECG, with onset between Day 1 and 15 of treatment. Overall, 9 patients (7.4%) have experienced a QT interval corrected using Fridericia's method (QTcF) > 500 ms.

Prolonged QTc is managed effectively by dose reduction, and all CO-1686 protocols contain patient selection criteria and specific guidance for the management of patients who develop prolonged QTc.

In summary, CO-1686 has a manageable safety profile at all doses evaluated.

Table 3-2: Treatment-related AEs Reported in at Least 5% of Patients or Treatment-related Events Associated with Inhibition of WT EGFR in Study CO-1686-008

Total Daily Dose	**< 1800 mg (N = 38)**	**1800 mg[a] (N = 19)**	**1000 mg (N = 18)**	**1250 mg (N = 17)**	**1500 mg (N = 50)**	**2000 mg (N = 6)**	**Total (N = 148)**
Formulation	FB	FB	HBr	HBr	HBr	HBr	
Frequency	Various[b]	900 mg BID	500 mg BID	625 mg BID	750 mg BID	1000 mg BID	
Overall n of patients with at least 1 TEAE	28 (73.7%)	18 (94.7%)	16 (88.9%)	15 (88.2%)	28 (56.0%)	6 (100.0%)	111 (75.0%)
Gastrointestinal Disorders							
Diarrhea	6 (15.8%)	6 (31.6%)	4 (22.2%)	4 (23.5%)	6 (12.0%)	2 (33.3%)	28 (18.9%)
Nausea	8 (21.1%)	6 (31.6%)	6 (33.3%)	7 (41.2%)	12 (24.0%)	3 (50.0%)	42 (28.4%)
Vomiting	5 (13.2%)	2 (10.5%)	3 (16.7%)	4 (23.5%)	4 (8.0%)	0	18 (12.2%)
General Disorders and Administrative Site Conditions							
Fatigue	9 (23.7%)	6 (31.6%)	5 (27.8%)	3 (17.6%)	5 (10.0%)	1 (16.7%)	29 (19.6%)
Investigations							
ECG QT prolonged	0	2 (10.5%)	0	2 (11.8%)	5 (10.0%)	3 (50.0%)	12 (8.1%)
Metabolism and Nutrition Disorders							
Glucose tolerance impaired/elevated glucose/hyperglycemia	4 (10.5%)	6 (31.6%)	11 (61.1%)	10 (58.8%)	14 (28.0%)	4 (66.7%)	49 (33.1%)
Decreased appetite	1 (2.6%)	6 (31.6%)	4 (22.2%)	3 (17.6%)	2 (4.0%)	2 (33.3%)	18 (12.2%)
Musculoskeletal and Connective Tissue Disorders							
Muscle spasms	3 (7.9%)	4 (21.1%)	3 (16.7%)	0	3 (6.0%)	0	13 (8.8%)
Myalgia	3 (7.9%)	4 (21.1%)	2 (11.1%)	0	1 (2.0%)	1 (16.7%)	11 (7.4%)
Skin and Subcutaneous Tissue Disorders							
Combined term for rash	0	0	1 (5.6%)	0	0	1 (16.7%)	2 (1.4%)

[a] 10 patients transitioned to 500 mg BID HBr on availability

[b] 150 mg to 900 mg QD, 100 mg to 600 mg BID, 400 mg TID

Study CO-1686-016

CO-1686-016 was a 3-part study in healthy male subjects which investigated the PK and safety of single and short course repeat doses of CO-1686 HBr salt. In this study, CO-1686 HBr was administered at single doses up to 1000 mg in the fasted state and at 500 mg BID in the fed state without significant adverse effects. Following CO-1686 HBr dosing over 4 days at 500 mg BID in a fed state, 3 of 6 healthy male subjects were noted to show asymptomatic increase in QTc on Day 4 of dosing which resolved when CO-1686 was discontinued.

3.2.2 Activity of CO-1686

CO-1686-008 is a 2-part, open-label, safety, PK, and preliminary efficacy study of CO-1686 in patients with advanced NSCLC. The dose escalation phase of the study has been completed.

Although the primary objectives of Phase 1 of study CO-1686-008 were to evaluate the safety, toxicity and PK profile of CO-1686, encouraging signals of activity have been observed in an EGFR mutation positive patient population previously treated with 1 of more lines of an EGFR-TKI (e.g., erlotinib, gefitinib, afatinib) and chemotherapy.

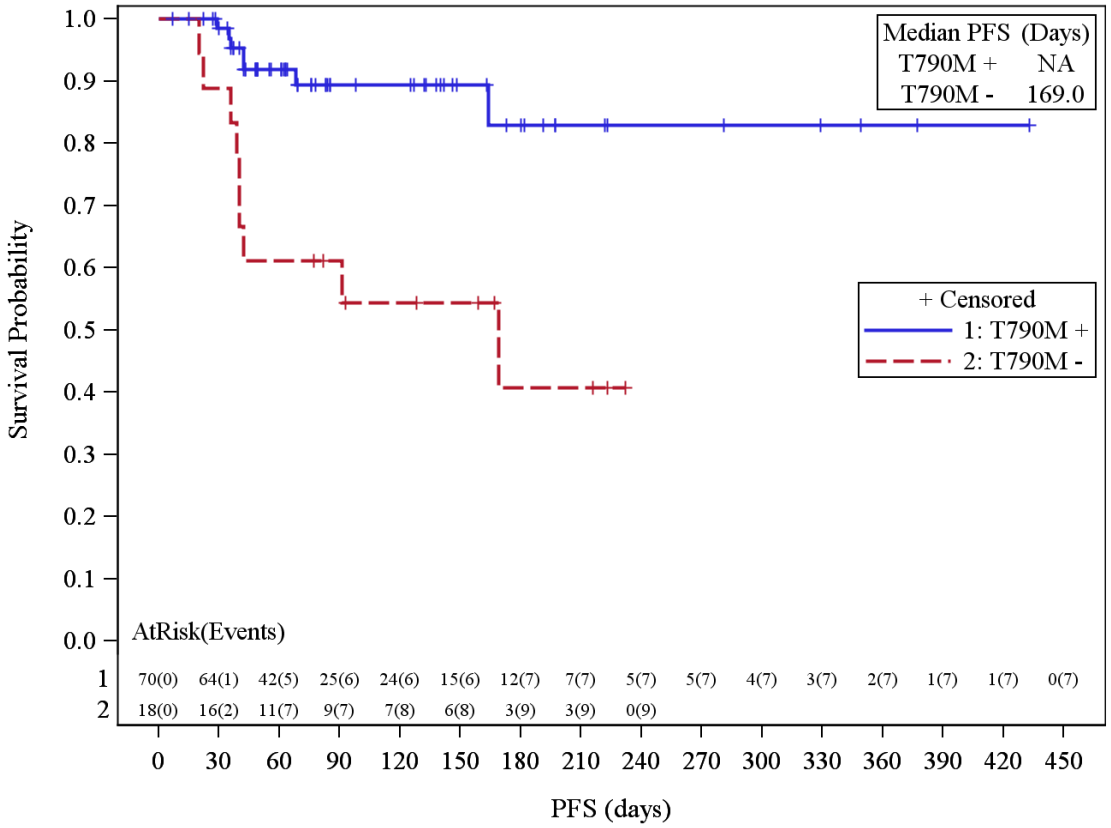
Response Evaluation Criteria in Solid Tumors (RECIST) response data are available for 40 patients with centrally confirmed T790M+ disease and are summarized in Table 3-3. The current objective response rate (ORR) is 55% and the disease control rate (DCR) is 93%. Median PFS has not been reached, but currently exceeds 12 months, and is shown in Figure 3-4. In patients with T790M negative disease, activity is more modest with a current median PFS of 169 days (Figure 3-4).

Table 3-3: Best Response, Objective Response, and Disease Control Rate in T790M+ Patients

	900 mg BID FB (N = 8)	500 mg BID HBr (N = 6)	625 mg BID HBr (N = 9)	750 mg BID HBr (N = 13)	1000 mg BID HBr (N = 4)	Overall (N = 40)
Best Response[a]						
PR	6 (75.0%)	3 (50.0%)	5 (55.6%)	5 (15.2%)	3 (75.0%)	22 (36.7%)
SD	2 (25.0%)	2 (33.3%)	2 (22.2%)	8 (24.2%)	1 (25.0%)	15 (25.0%)
PD	0 (0.0%)	1 (16.7%)	2 (22.2%)	0 (0.0%)	0 (0.0%)	3 (5.0%)
End of Cycle 2 scan not yet reached	0 (0.0%)	0 (0.0%)	0 (0.0%)	20 (60.6%)	0 (0.0%)	20 (33.3%)
Objective Response[a, b] **(CR, PR)**	6 (75.0%)	3 (50.0%)	5 (55.6%)	5 (38.5%)	3 (75.0%)	22 (55.0%)
Disease Control Rate[a, b] **(CR, PR, SD)**	8 (100.0%)	5 (83.3%)	7 (77.8%)	13 (100.0%)	4 (100.0%)	37 (92.5%)

[a] Data shown are for patients with measurable disease at baseline
[b] Percentage based on patients with non-missing best response

Figure 3-4: Kaplan-Meier Curves of Progression-free Survival by T790M Status for 900 mg BID Free Base and All HBr Patients



3.2.3 Pharmacokinetics of CO-1686 HBr

Study CO-1686-016

In healthy volunteers (Study CO-1686-016), maximum concentration (C_{max}) and area under the curve from time zero to 24 hours ($AUC_{0–24}$) of CO-1686 increased with ascending single doses of the CO-1686 HBr formulation (50 mg to 1000 mg), with CO-1686 plasma levels increasing in a less than dose proportional manner above 125 mg.

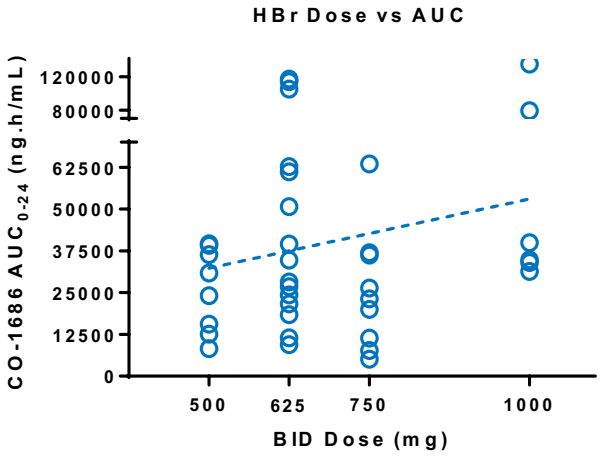
The single dose PK of CO-1686 HBr was compared in the fasted and fed state, and it was concluded that a high-fat meal increased the plasma drug concentrations from 3 to 12 hours postdose with a mean increase of 172% at 12 hours postdose (C_{12h}: –22% to +400%) and a mean increase of 77% in $AUC_{0–24}$ (+10% to 146%) with no change in elimination half-life ($T_{1/2}$); a slight mean increase of 12% in C_{max} was observed and a delayed time to maximum concentration (T_{max}) was seen in a majority of subjects.

Six healthy subjects were dosed, in the fed state, with 500 mg BID CO-1686 HBr for 4 days. PK profiles of CO-1686 following morning and evening dosing were similar, with low intra-subject variability (Day 1 and Day 4 comparison). There was no accumulation of CO-1686.

Study CO-1686-008

In the patient study (CO-1686-008), PK following HBr salt administration were available from a total of 44 patients (4 started at 500 mg BID, 10 switched from CO-1686 free base to 500 mg BID HBr, 15 started at 625 mg BID, 9 started at 750 mg BID, and 6 started at 1000 mg BID). CO-1686 HBr showed increased absorption and thus, higher exposure than free base. The median T_{max} was 2 to 3.25 hrs and $T_{1/2}$ ranged from 1.7 to 4.7 hrs. Following CO-1686 HBr administration, exposure (measured as C_{max} and AUC_{0-24}) increased dose-proportionally from 500 mg to 1000 mg BID (Figure 3-5).

Figure 3-5: Individual CO-1686 AUC_{0-24} on Day 1 Following 500 mg to 1000 mg CO-1686 HBr BID



3.3 Rationale for Study

NSCLC patients whose tumors have mutations in the EGFR gene experience improved clinical outcomes with EGFR-targeted therapy as compared to chemotherapy. Clinical improvements notwithstanding, patients receiving EGFR-directed therapy experience significant skin rash and diarrhea related to inhibition of the WT EGFR in skin and intestine, respectively.[5,6,8] While efficacy is improved with EGFR-TKIs relative to chemotherapy, median PFS is only in the 10-month range. New therapies that provide longer PFS and provide a tolerable side effect profile are needed.

CO-1686 effectively targets both the most common activating EGFR mutations and the most common mutation driving EGFR resistance, T790M, but spares the WT EGFR receptor. The hypothesis is that CO-1686 will drive more durable disease control in the first-line setting, through inhibition of the activating mutations and suppression of T790M development, with improved tolerability owing to lack of WT EGFR effects.

4 STUDY OBJECTIVES AND ENDPOINTS

The objectives and corresponding endpoints of the study are as follows:

4.1 Objectives

4.1.1 Primary Objective

- To compare the antitumor efficacy of oral single-agent CO-1686 with that of erlotinib as measured by PFS, when administered as a first-line targeted treatment to patients with EGFR-mutated, advanced/metastatic NSCLC

4.1.2 Secondary Objectives

- To compare secondary measures of clinical efficacy (ORR, DR, and OS) of oral single-agent CO-1686 with that of erlotinib when administered as a first-line targeted treatment in patients with advanced/metastatic NSCLC whose tumors have EGFR-activating mutations
- To assess PFS, ORR, DR, and OS in patients with baseline T790M mutations based on central allele-specific polymerase chain reaction (PCR) EGFR mutation assay
- To assess quality of life (QOL) using the patient-reported outcomes (PRO) of European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) and the EORTC Quality of Life Questionnaire Lung Cancer module (EORTC QLQ-LC13),[15] the Dermatology Life Quality Index (DLQI),[16] and the EQ-5D instrument[17] in patients receiving treatment with CO-1686 versus erlotinib
- To evaluate safety and tolerability of CO-1686 versus erlotinib in patients with advanced/metastatic NSCLC whose tumors have EGFR-activating mutations
- To determine PK of CO-1686 in this patient population using population PK (POPPK) methods and explore correlations between PK, exposure, response, and/or safety findings

4.1.3 Exploratory Objectives

- To compare DCR of oral single-agent CO-1686 with that of erlotinib when administered as a first-line targeted treatment in patients with advanced/metastatic NSCLC whose tumors have EGFR-activating mutations
- To assess DCR in patients with baseline T790M mutations based on central allele-specific PCR EGFR mutation assay
- To compare kinetics of tumor growth between treatment arms measured by rate of change in sum of the longest diameters of target lesions (SLD) or rate of change of estimated or measured assessments of tumor volume
- To compare efficacy between treatment arms in patients with baseline T790M+ disease, detected using an ultra-sensitive research assay
- To compare the effect between treatment arms in patients who develop progressive disease (PD) while on study treatment but continue to receive assigned study treatment with CO-1686 or erlotinib beyond progression

- To evaluate concordance of EGFR mutation detection between patient tissue and plasma and to assess CO-1686 or erlotinib mediated alterations in levels of EGFR mutation detected using circulating tumor DNA (ctDNA) obtained from patient plasma
- To explore tissue and blood-based biomarkers that may be predictive of response or primary resistance to CO-1686 or erlotinib and investigate mechanisms of acquired resistance to treatment with CO-1686 or erlotinib using patient tumor tissue and blood samples

4.2 Endpoints

4.2.1 Primary Endpoints

- PFS according to RECIST Version 1.1 as determined by investigator review (invPFS)

4.2.2 Secondary Endpoints

- ORR, and DR, according to RECIST Version 1.1 as determined by investigator review, and OS
- invPFS, ORR, DR, and OS in patients with baseline T790M mutations confirmed by central EGFR mutation assay
- Change from baseline in QOL as measured using the PRO of EORTC QLQ-C30, EORTC QLQ-LC13, the DLQI, and the EQ-5D following treatment with CO-1686 versus erlotinib
- Treatment-emergent AEs, laboratory abnormalities and ECG abnormalities
- Plasma PK parameters for CO-1686 based on sparse sampling

4.2.3 Exploratory Endpoints

- DCR according to RECIST Version 1.1 as determined by investigator review
- DCR in patients with baseline T790M mutations confirmed by central EGFR mutation assay
- Rate of change in SLD
- Rate of change in tumor volume (measured or modeled)
- InvPFS, ORR, DR, DCR, time-to-treatment failure, and OS in patients who develop PD while on study treatment but continue to receive assigned study treatment with CO-1686 or erlotinib beyond progression
- Concordance of tumor and plasma ctDNA mutational analysis using contemporaneous samples
- Time from randomization to second observed increase over nadir in plasma mutant EGFR ctDNA levels (activating mutation, T790M mutation, either or both)
- Fraction of patients exhibiting disappearance of mutant EGFR ctDNA after initiating treatment with CO-1686
- Change from baseline in other tissue and blood biomarkers associated with the EGFR signaling pathways and relationship with clinical efficacy outcomes

5 STUDY DESIGN

5.1 Overall Study Design and Plan

This is a randomized, open-label, Phase 2/3 study of CO-1686 versus erlotinib as a first-line treatment for patients with advanced/metastatic NSCLC whose tumors have EGFR-activating mutations. The study will consist of Phase 2 and Phase 3 parts which will use the same enrollment criteria and treatment assignment principles. The Phase 2 part is an open-label study; in the Phase 3 part, the sponsor will be blinded to efficacy and safety results aggregated by randomized treatment group. The Phase 2 part will enroll approximately 200 patients. Data from the Phase 2 part will be used to inform on the sample size in the Phase 3 part of the study. The sample size of the Phase 3 component will be capped at approximately 1,000 patients. The Phase 3 part will include up to 3 interim analyses. At each interim analysis, enrollment into the Phase 3 part may be stopped if there is a high probability of success in the Phase 3 part of the study. If enrollment is stopped early, the Phase 3 part of the study will continue until at least 70% of the randomized patients have a PFS event.

Patients will be stratified for randomization according to the followings factors:

- Sensitizing EGFR mutation (L858R, del19, or other)
- Territory of residence at time of randomization (Asia or non-Asia)

Patients will be randomized in a 1:1 ratio to Treatment Arm #1 or #2:

- Treatment Arm #1 – CO-1686, 500 mg orally (PO), with food, BID
- Treatment Arm #2 – erlotinib, 150 mg PO, on an empty stomach, once daily (QD)

5.1.1 Screening Period

Patients will undergo screening assessments within 35 days prior to the first day of dosing (C1D1). AEs will be collected from the time the first dose of CO-1686 or erlotinib is administered through 28 days after the last dose. Study procedure-related AEs that occur after signing of the Informed Consent Form (ICF) and before administration of CO-1686 or erlotinib will also be captured. Certain screening assessments are required to be performed closer to the time of dosing than others. Please see study procedures (Section 9) for details.

5.1.2 Treatment Period

Patients will receive either CO-1686 or erlotinib. The sponsor will be blinded to efficacy and safety results aggregated by randomized treatment group in the Phase 3 part of the study. CO-1686 will be administered to patients as 500 mg PO tablets on a BID basis with a meal or within 30 minutes after a meal (see Section 7.3). Erlotinib will be taken 150 mg PO QD on an empty stomach; i.e., at least 1 hour before or 2 hours after the ingestion of food (see Section 7.3). Treatment with CO-1686 or erlotinib is continuous. Dosing will be delayed or reduced according to protocol-specified toxicity criteria (See Section 7.4).

Patients will undergo serial assessments for anti-tumor efficacy, drug safety, PK, PRO, and biomarkers. Sparse blood sampling for population PK analyses will be conducted in all patients initially randomized and treated with CO-1686. Serial blood sampling for longitudinal quantitative assessment of ctDNA will be conducted on all patients in the study. All patients will provide a tumor biopsy during screening for determination of EGFR mutation status. For both the Phase 2 and 3 parts, local laboratory testing will be used to determine the presence of an activating EGFR mutation. EGFR mutation status will be confirmed by central testing retrospectively.

ECGs will be performed and interpreted locally for patient care decisions; however, tracings will be collected centrally for independent evaluation. Tissue and blood specimens from both treatment arms will be used to explore biomarkers that may be predictive of response or primary resistance to CO-1686 and/or erlotinib. AEs will be collected from the time the first dose of CO-1686 or erlotinib is administered through 28 days after the last dose. Local laboratories will be used for hematology, chemistry, and urinalysis.

QOL questionnaires (EORTC QLQ-C30, EORTC QLQ-LC13, the DLQI, and the EQ-5D) will be collected at screening, predose on C1D1, then every 8 ± 1 weeks for the first 6 months (Day 1 of Cycles 3, 5, 7); after Cycle 7, questionnaires will be collected every 12 ± 1 weeks (Day 1 of Cycles 10, 13, 16, etc.) and at end-of-treatment. In the Phase 2 part only, patients participating in the crossover portion will be asked to complete QOL questionnaires mirroring the on-study assessment schedule.

Tumor assessments will be performed by the investigative site and scans will be evaluated locally for patient treatment decisions. Scans will also be collected, quality control performed, and stored with a central vendor; central reading of scans will not be done unless requested by the sponsor. Patients will be scanned at screening and every 8 ± 1 weeks (Day 1 of Cycles 3, 5, 7, etc.) until there is radiographically-confirmed PD according to RECIST Version 1.1. If clinical progression is suspected, the confirmation of PD with a computed tomography (CT) scan or by magnetic resonance imaging (MRI) per RECIST Version 1.1 will be required. Patients who provide an optional additional consent will undergo tumor biopsy on progression and before subsequent-line therapy is initiated. Phase 2 patients randomized to the erlotinib treatment arm and who choose to participate in the crossover portion of the study after progression and are eligible to receive CO-1686, will undergo their optional biopsy after progression during the crossover. When protocol-specified therapy is discontinued, and the patient has yet to progress, patients will continue to undergo scheduled tumor assessments for monitoring of PFS. For all patients, after discontinuation of protocol-specified treatment, subsequent specific anticancer therapy used at the investigator's discretion will be recorded.

EGFR-inhibitor therapy is commonly continued beyond disease progression if the patient appears to be experiencing benefit in the investigator's opinion and this convention will be applied in this study. Patients may opt to continue to receive treatment with CO-1686 following radiographic progression as outlined in the National Comprehensive Cancer Network (NCCN) guidelines for treatment of NSCLC with EGFR-TKIs[18] if: a) the patient provides additional consent, b) the investigator feels it is in the patient's best interest, and c) the sponsor provides approval. In general, eligible patients may include those with asymptomatic systemic progression or locally symptomatic progression, such as brain metastases amenable to local treatment, with

concomitant asymptomatic systemic progression or continued systemic disease control. Patients randomized to the erlotinib arm may also continue to be treated post-progression with erlotinib if this agent is to be continued as a single agent. Palliative radiation therapy intended to provide relief of cancer-related symptoms is permitted while the patient is on study, as long as there is no evidence of disease progression per RECIST Version 1.1. Such palliative radiotherapy must be approved prospectively by the sponsor and documented in the electronic case report form (eCRF). If the erlotinib dose is to be escalated or other agents are to be added in, the patient must be discontinued from the study, perform End-of-Treatment Visit procedures, and continue to the follow-up portion of the study. Any patient on this study who is to be treated post-progression must be discussed with the sponsor, and will be reviewed on a case-by-case basis. If a patient continues treatment with CO-1686 or erlotinib post-progression, all study assessments including efficacy assessments, safety assessments, QOL administration, and blood collection for biomarker analysis and exploratory research should continue per protocol. The patient should be discontinued from treatment once it is clear that no further clinical benefit can be achieved.

In the Phase 2 part only, for patients initially randomized to erlotinib, there is an optional crossover phase following disease progression per RECIST Version 1.1 and confirmation of T790M+ disease by local laboratory using tissue sample collected after disease progression. Patients who progress on erlotinib who have not developed the T790M mutation are not eligible to receive CO-1686 in the crossover part of the study, because for these patients, progression on erlotinib is likely driven by other mechanisms that are unlikely to respond to CO-1686. Patients in the crossover phase will continue all study assessments including efficacy assessments, safety assessments, QOL administration, and blood collection for biomarker analysis and exploratory research as outlined in Section 9.3.

5.1.3 End-of-Treatment

All patients should return to the study site for the End-of-Treatment Visit assessments 28 (± 7) days after the last dose of PO CO-1686 or erlotinib has been administered. In the Phase 2 part only, patients participating in the crossover phase will undergo the End-of-Treatment Visit once, only after discontinuation of crossover CO-1686 treatment. Tumor assessments should be performed at the End-of-Treatment Visit if radiographic disease progression has not been documented previously. An MRI may be used in place of a CT as end-of-treatment scan if required per local authorities.

The treatment phase of the trial will be completed when all enrolled patients have discontinued treatment and completed the End-of-Treatment Visit procedures.

5.1.4 Three Monthly Follow-up

Upon discontinuation of original study treatment, or crossover phase (Phase 2 only), all patients will enter the follow-up phase to monitor for survival status and subsequent NSCLC therapy approximately every 3 months (12 ± 1 weeks) until death or sponsor decision, whichever comes first. For patients who discontinue treatment without progression, tumor scans will be performed every 8 ± 1 weeks until disease progression occurs.

5.1.5 Extension Phase

In mid-2015, Clovis submitted a New Drug Application for the use of CO-1686 in patients with T790M-positive NSCLC. In June 2016, the FDA issued a Complete Response Letter to Clovis stating that more data are required to approve CO-1686 for use outside of a clinical trial. Based on this outcome, Clovis decided to discontinue development of CO-1686 for NSCLC. Patients will be informed of this change in the development plans in an update to the informed consent form for this study. Those patients who continue to derive clinical benefit from study treatment will be allowed to continue on study at the discretion of the Principal Investigator in an extension phase.

The purpose of this protocol amendment is to add a new Extension Phase to allow patients to continue on study but to avoid unnecessary collection of data that will no longer be analyzed or required for regulatory purposes, whilst maintaining an appropriate level of safety monitoring. A new schedule of assessments for the Extension Phase as well as a complete description of procedures has been provided in Appendix D. This schedule will replace all schedules of assessments in Section 9 Study Procedures and should be followed for all patients.

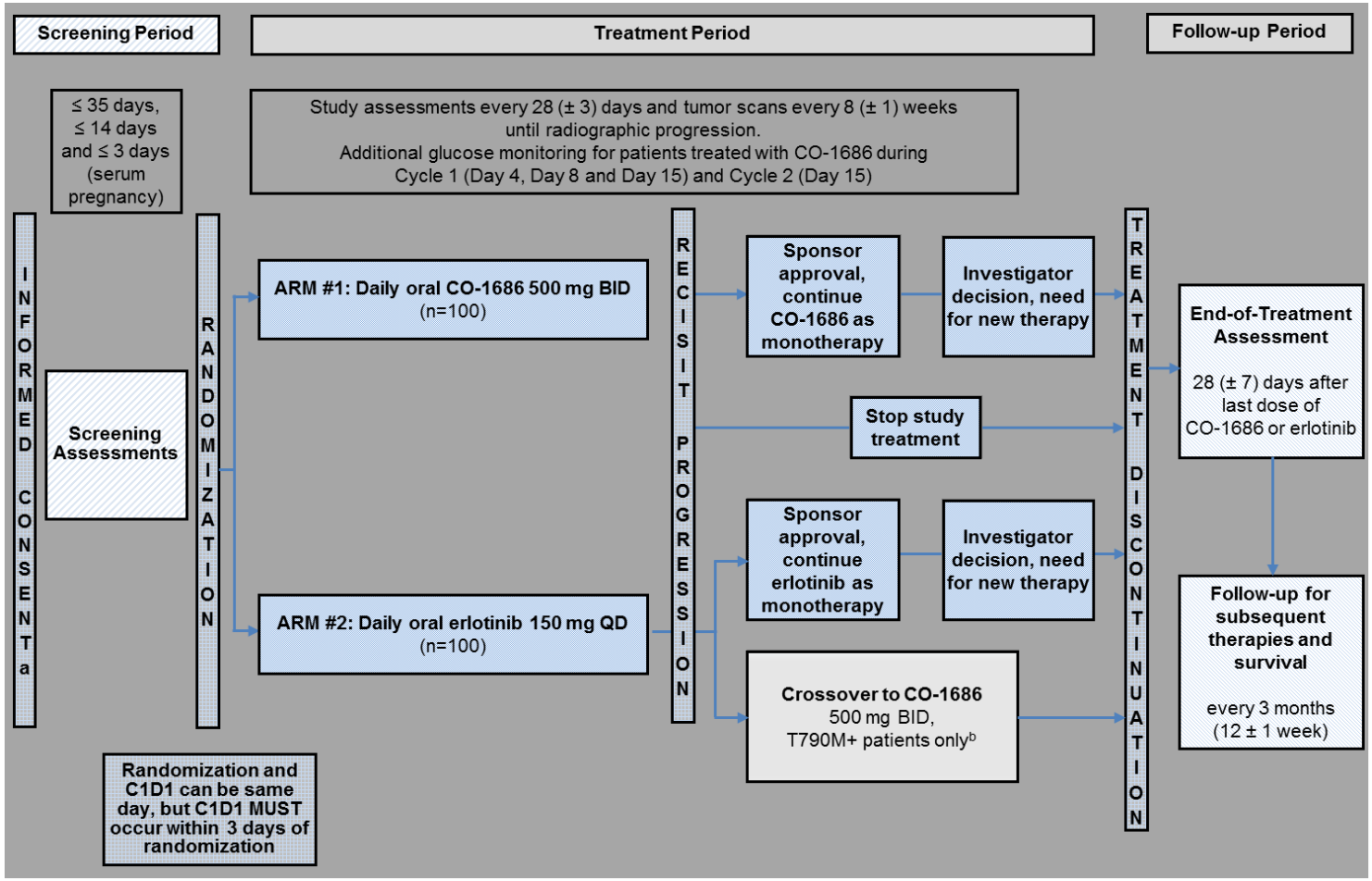
An important change of the Extension phase is the removal of the option for patients to crossover to CO-1686 following radiographic progression on erlotinib. The decision to remove the crossover option to CO-1686 was based on the recommendation of the DMC, which oversees the risk/benefit aspects of the study. Patients and their physicians are directed to seek alternative treatments, which can fulfill this need.

For patients who wish to continue CO-1686 or erlotinib treatment post progression it is important that a full exploration of alternative treatment options between patients and their treating physicians takes place.

5.2 Study Schema

The study schemas in Figure 5-1 and Figure 5-2 summarize the treatment design of the study for the Phase 2 and Phase 3 parts, respectively.

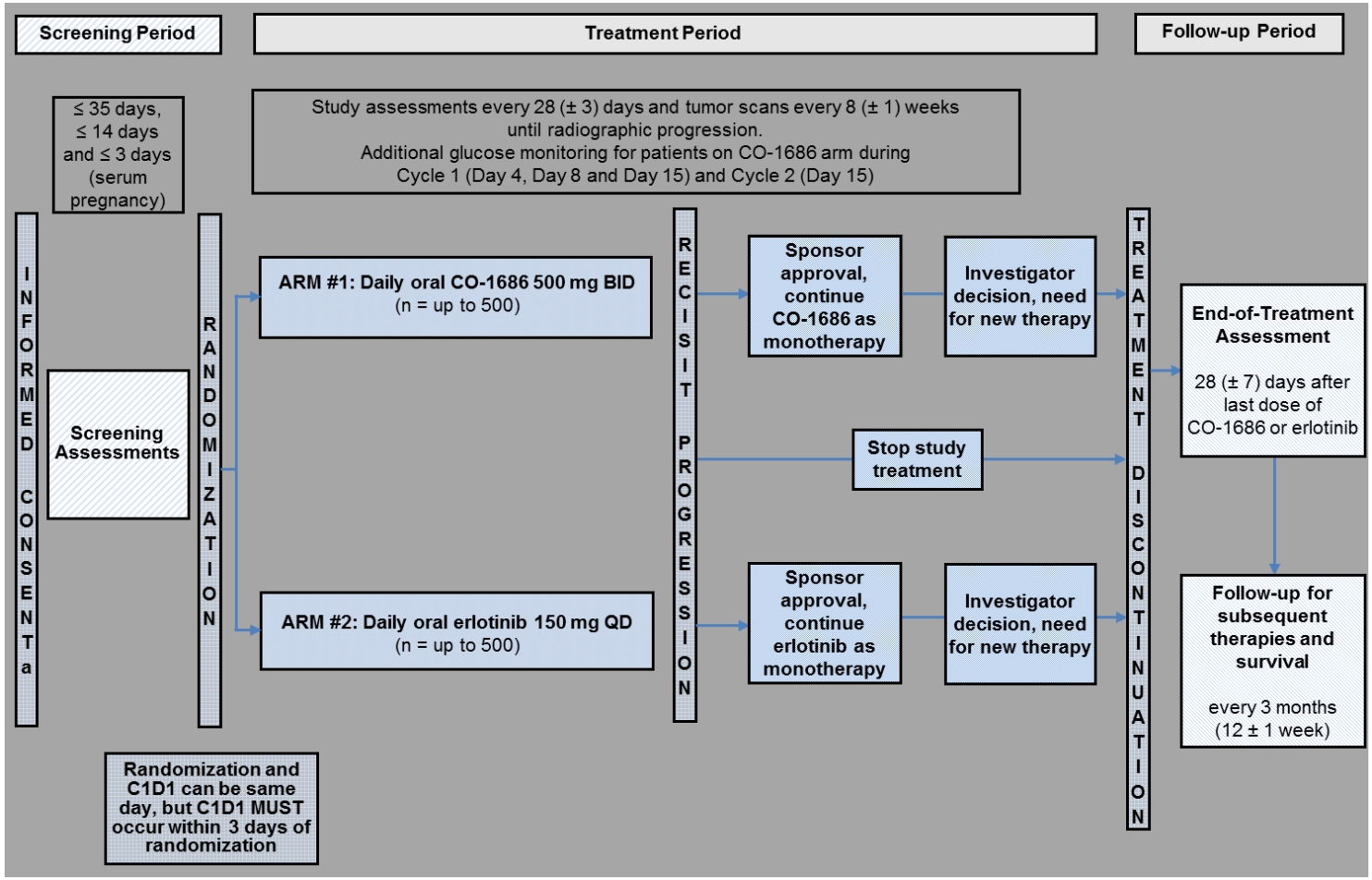
Figure 5-1: Study Schema (Phase 2 Part)



[a] ICF signature required before any protocol specific assessments, but signature of ICF does not start screening period timing. The first screening activity performed after ICF signature will begin the 35 day screening period. If a procedure is completed greater than 35 days prior to the first day of dosing, it will need to be repeated prior to C1D1 unless otherwise specified. If a standard-of-care biopsy was performed within 60 days of C1D1, and no intervening treatment was given, a repeat biopsy is not required if adequate tumor tissue can be provided for eligibility assessments.

[b] Other eligibility criteria also apply (see Section 9.3).

Figure 5-2: Study Schema (Phase 3 Part)



[a] ICF signature required before any protocol specific assessments, but signature of ICF does not start screening period timing. The first screening activity performed after ICF signature will begin the 35 day screening period. If a procedure is completed greater than 35 days prior to the first day of dosing, it will need to be repeated prior to C1D1 unless otherwise specified. If a standard-of-care biopsy was performed within 60 days of C1D1, and no intervening treatment was given, a repeat biopsy is not required if adequate tumor tissue can be provided for eligibility assessments.

6 STUDY POPULATION

6.1 Number of Patients and Sites

The total enrollment planned for this study is approximately 1,200 patients.

Patients will be randomized in the ratio 1:1 to treatment with CO-1686 or erlotinib (for each treatment arm: approximately 100 patients in the Phase 2 part and up to 500 patients in the Phase 3 part).

Approximately 95 investigative sites will be open globally.

6.2 Inclusion Criteria

All patients must meet all of the following inclusion criteria:

1. Histologically or cytologically confirmed metastatic or unresectable locally advanced/metastatic NSCLC

2. Documented evidence of a tumor with activating EGFR mutations by local testing

    - Patients with exon 20 insertions are not eligible with the exception of patients with documented evidence of the exon 20 insertion A763_Y764insFQEA in the EGFR gene

3. Have undergone a biopsy or surgical resection of either primary or metastatic tumor tissue within 60 days of the first day of study treatment, C1D1, and have tissue available to send to sponsor laboratories or are able to undergo a biopsy during screening and provide tissue to sponsor laboratories

4. Measureable disease according to RECIST Version 1.1

5. Life expectancy of at least 3 months

6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1

7. Age ≥ 18 years (in certain territories, the minimum age requirement may be higher; e.g., age ≥ 20 years in Japan and Taiwan)

8. Adequate hematological and biological function, confirmed by the following laboratory values:

    - Bone Marrow Function
        - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
        - Platelets > 100.0 × 10^9/L
        - Hemoglobin ≥ 9 g/dL (or 5.6 mmol/L)

- Hepatic Function
  - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 × upper limit of normal (ULN); if liver metastases, ≤ 5 × ULN
  - Bilirubin ≤ 2 × ULN (Patients with documented Gilbert's syndrome and conjugated bilirubin within normal range may be allowed into the study. In this event, it will be documented that the patient was eligible based on conjugated bilirubin levels)
- Renal Function
  - Serum creatinine ≤ 1.5 × ULN
- Electrolytes
  - Potassium and magnesium within normal range, patients may receive supplements to meet this requirement

9. Written informed consent on an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved ICF prior to any study-specific evaluation

6.3 Exclusion Criteria

Any of the following criteria will exclude patients from study participation:

1. Documented evidence of an exon 20 insertion activating mutation other than A763_Y764insFQEA in the EGFR gene

2. Prior treatment with cytotoxic chemotherapy for advanced NSCLC; neoadjuvant/adjuvant chemotherapy is permitted if at least 6 months has elapsed between the end of chemotherapy and randomization

3. Active second malignancy; i.e., patient known to have potentially fatal cancer present for which he/she may be (but not necessarily) currently receiving treatment
   - Patients with a history of malignancy that has been completely treated, and currently with no evidence of that cancer, are permitted to enroll in the trial provided all chemotherapy was completed > 6 months prior and/or bone marrow transplant > 2 years prior to first day of study treatment, C1D1

4. Known pre-existing interstitial lung disease (ILD)

5. Brain metastases

6. Treatment with prohibited medications (e.g., concurrent anticancer therapy including other chemotherapy, radiation, hormonal treatment [except corticosteroids and megesterol acetate], or immunotherapy) ≤ 14 days prior to first day of study treatment, C1D1

7. Patients who are currently receiving treatment with any medications that have the potential to prolong the QT interval if that treatment cannot be either discontinued or switched to a different medication (not known to affect QT interval) prior to C1D1

- See http://crediblemeds.org/ for a current list of QT-prolonging medications

8. Prior treatment with EGFR-TKIs (e.g., erlotinib, gefitinib, neratinib, afatinib, AZD9291, or dacomitinib), CO-1686, or other drugs that target mutant EGFR

9. Any of the following cardiac abnormalities or history
   - Clinically significant abnormal 12-lead ECG, QT_CF > 450 ms
   - Inability to measure QT interval on ECG
   - Personal or family history of long QT syndrome
   - Implantable pacemaker or implantable cardioverter defibrillator
   - Resting bradycardia < 55 beats/min

10. Non-study related surgical procedures ≤ 7 days prior to C1D1. In all cases, the patient must be sufficiently recovered and stable before treatment administration.

11. Females who are pregnant or breastfeeding

12. Refusal to use adequate contraception for fertile patients (females and males) during study treatment and for 12 weeks after the last dose of CO-1686 and 2 weeks after the last dose of erlotinib

13. Presence of any serious or unstable concomitant systemic disorder incompatible with the clinical study (e.g., substance abuse, uncontrolled intercurrent illness including uncontrolled diabetes, active infection, arterial thrombosis, and symptomatic pulmonary embolism)

14. Any other reason the investigator considers the patient should not participate in the study

6.4 Patients or Partners of Patients of Reproductive Potential

Pregnancy is an exclusion criterion and women of childbearing potential must not be considering getting pregnant during the study. Female patients who are more than 2 years postmenopausal or have had a hysterectomy will not be considered of childbearing potential. Female patients of childbearing potential must have a negative serum pregnancy test ≤ 3 days prior to the first day of dosing (C1D1). If the serum pregnancy test results are not available at C1D1, a urine pregnancy test can be performed on that day to confirm that the patient is not pregnant prior to dosing. Both values should be entered in the eCRF. Another serum pregnancy test will be performed at the End-of-Treatment Visit.

Patients of reproductive potential (males and females) must practice double-barrier methods of contraception during treatment and for 12 weeks following the last dose of CO-1686 and for 2 weeks after last dose of erlotinib. Adequate contraception is defined as abstinence or double-barrier protection; i.e., condom plus spermicide in combination with a diaphragm, cervical/vault cap, or intrauterine device. Birth control pills, birth control patches and/or injections of hormones to prevent pregnancy are not considered an adequate method of preventing pregnancy, and double-barrier protection is required while on study and for 12 weeks (CO-1686) or 2 weeks (erlotinib) after last dose.

Patients will be instructed to notify the investigator if pregnancy is discovered either during or within 12 weeks of completing treatment with CO-1686, or during or within 2 weeks of completing treatment with erlotinib. This also applies to male patients whose partners become pregnant while the patient is on study, or within the 12-week period after the last dose of CO-1686 or the 2-week period after the last dose of erlotinib.

6.5 Waivers of Inclusion/Exclusion Criteria

No waivers of these inclusion or exclusion criteria will be granted by the investigator and the sponsor or its designee for any patient enrolling into the study.

7 DESCRIPTION OF STUDY TREATMENTS AND DOSE MODIFICATIONS

7.1 Description of Study Treatments

7.1.1 CO-1686

CO-1686 is provided as yellow, film-coated tablets for oral administration in two dosage strengths made from the same drug blend. The strengths are achieved by adjusting the total tablet weight. The strengths are differentiated by tablet shapes: 125 mg strength is a round tablet and 250 mg strength tablet is an oval tablet. Each tablet consists of CO-1686 HBr drug substance, silicified microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, copovidone, magnesium stearate and hypromellose based film coat. Excipients used are generally regarded as safe (GRAS). Tablets are packaged along with desiccant in high density polyethylene bottles closed with a child-resistant cap. Tablets will be supplied to the study sites by the sponsor. CO-1686 tablets should be stored in their original packaging at 15°C to 30°C (59°F to 86 F).

Child-resistant bottles containing CO-1686 tablets are labeled according to applicable regulations for investigational products. Patients should be advised not to split or crush tablets. Additionally, patients should be advised not to take tablets with chips or other gross visual defects. Defective tablets should be returned to the study site.

7.1.2 Erlotinib

Erlotinib is a white to yellowish, film-coated tablet containing erlotinib hydrochloride, for daily administration; the 150 mg dose strength will be used in this study. If necessary for dose reductions or based on availability, 100 mg and 25 mg dose strengths of erlotinib may also be used.

Commercially available erlotinib (blister packs) will be either procured by investigative sites or supplied by the sponsor.

7.2 Method of Assigning Patients to Treatment Groups

Following confirmation of patient eligibility by the sponsor, patients will be centrally randomized in the ratio 1:1 to receive oral CO-1686 or erlotinib. Patients will be stratified according to presence of sensitizing EGFR mutation (L858R, del19, or other) and territory of residence at time of randomization (Asia vs non-Asia).

The treatment assignment will be generated using the following procedure to ensure that treatment assignment is unbiased. A patient randomization list will be produced by the Interactive Voice/Web Response System (IVRS/IWRS) provider using a validated system that automates the random assignment of treatment. The investigator or his/her delegate will call or log on to the IVRS/IWRS and confirm that the patient fulfills all the inclusion/exclusion criteria. Each package of study drug will contain the unique identification code containing the LOT number and a space for the site to enter the "Subject ID".

Treatment should be initiated on C1D1, which must occur within 3 days (72 hours) of randomization.

7.3 Preparation and Administration of Protocol-specified Treatment

7.3.1 CO-1686

CO-1686 will be administered PO at 500 mg BID. Patients should take CO-1686 as directed by the study investigator. Each dose should be taken with 8 oz (240 mL) of water and with a meal or within 30 minutes after a meal. Tablets should be swallowed whole.

If a patient misses a dose (i.e., does not take it within 6 hours of the scheduled time), he or she should resume taking CO-1686 with their next scheduled dose. Missed or vomited doses will not be made up.

The investigator or designee will be responsible for distributing the appropriate strength(s) of oral CO-1686 tablets to all patients. A sufficient number of tablets will be provided to the patient to last until the next scheduled visit. Patients will be instructed to record daily doses taken or not taken on a patient diary, and will be instructed to bring their CO-1686 tablets and diary to the next scheduled visit for reconciliation by site personnel.

7.3.2 Erlotinib

Erlotinib 150 mg will be administered PO QD according to the prescribing information.[19] Treatment with erlotinib is continuous. Patients should take erlotinib as directed by the study investigator. Each dose should be taken with 8 oz (240 mL) of water on an empty stomach; i.e., at least 1 hour before or 2 hours after the ingestion of food.

If a patient misses a dose (i.e., does not take it within 6 hours of the scheduled time), he or she should resume taking erlotinib with their next scheduled dose. Missed or vomited doses will not be made up.

The investigator or designee will be responsible for distributing erlotinib to patients. A sufficient number of tablets will be provided to the patient to last until the next scheduled visit. Patients will be instructed to record daily doses taken or not taken on a patient diary, and will be instructed to bring their erlotinib tablets and diary to the next scheduled visit for reconciliation by site personnel.

7.4 Dose Modifications of Protocol-specified Treatment

7.4.1 CO-1686

No dose escalation above the starting dose is allowed. Two dose reduction steps are allowed for each patient. The dose reductions are from 500 mg BID (starting dose) to 375 mg BID, then to 250 mg BID. The dose of CO-1686 should not be reduced below 250 mg BID without prior sponsor approval.

For National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 Grade 3 or 4 hematologic and non-hematologic toxicities (except for nausea/vomiting, alopecia, QTc prolongation and hyperglycemia), the dose should be initially reduced to 375 mg BID and, if persistent, to 250 mg BID for subsequent doses if the investigator and sponsor do not believe treatment discontinuation is required. Re-escalation of dose after resolution of AEs must be discussed and approved by sponsor prospectively.

Once the dose has been reduced, treatment continues at that dose level until the next visit; no dose escalation is possible between visits. If a patient continues to experience toxicity after 2-dose reductions, or if dosing with CO-1686 is interrupted for > 14 consecutive days due to toxicity, treatment should be discontinued unless otherwise agreed between the investigator and the sponsor before reintroduction of study drug.

Management of Prolonged QTc

ECGs will be measured throughout the study as described in the protocol. Readings for QTc prolongation will be based on the average seen in the ECGs for each time point. Patients are required to have laboratory values for potassium and magnesium within normal limits at enrollment, and these electrolytes should be maintained within range during CO-1686 treatment, if necessary using supplementation. If QT_C prolongation of CTCAE Grade 3 is observed, CO-1686 will be held until the event has improved to Grade 1. CO-1686 can then be re-started at a reduced dose upon approval by sponsor. After 2 dose reductions, if CTCAE Grade 3 or above QT_C prolongation recurs, then CO-1686 will be discontinued unless agreed with the sponsor that additional dose reduction may be considered. If QT_C prolongation changes of CTCAE Grade 4 are observed at any time, CO-1686 will be discontinued permanently.

Management of Hyperglycemia

CO-1686 causes hyperglycemia in some patients secondary to inhibition of the insulin-like growth factor 1 receptor (IGF-1R) and insulin receptor (IR) kinases by a metabolite. Therefore, some patients will require addition of a glucose lowering medication and patients with pre-existing diabetes may require more frequent monitoring and/or adjustments of diabetic medication. Clinical experience with CO-1686 suggests hyperglycemia generally occurs within the first 3 weeks of treatment, leading to the need for more intensive glucose monitoring during the first several weeks of the study. In Phase 1/2 clinical trial experience, increased nausea, vomiting, decreased appetite, diarrhea, muscle cramps and fatigue have been reported in patients with hyperglycemia. Such patients must be closely monitored including assessment of fasting glucose levels and early initiation of anti-hyperglycemic therapy. As CO-1686-induced hyperglycemia is mediated through insulin resistance, agents that suppress glucose synthesis (metformin), increase sensitivity to insulin (glitazones) or increase glucose excretion (sodium- glucose cotransporter 2 [SGLT2] inhibitors) are expected to be more effective than those that increase plasma insulin (sulphonylureas or exogenous insulin). Metformin has been used most frequently in CO-1686 clinical studies and is, therefore, recommended as the initial agent to manage hyperglycemia in patients with normal renal function. In addition, preliminary data from the ongoing Study CO-1686-008 suggest that starting metformin at the same time CO-1686 therapy is initiated may prevent development of CO-1686-induced hyperglycemia. For all patients, irrespective of whether they are receiving metformin prophylactically or therapeutically, glucose monitoring should be conducted according to the following schedule:

- Fasting glucose will be measured at the following visits: screening, C1D1, C1D4 (± 1 day), C1D8 (± 1 day), C1D15 (± 1 day), C2D1, C2D15 (± 1 day), C3D1, C4D1, C5D1, CND1 and End-of-Treatment Visit.

The following guidelines for management of hyperglycemia are based on experience in the Phase 1 study. Whilst the blood glucose thresholds for intervention outlined below should be followed, management of individual patients should be based on local practices and the treating physician's

judgment. In all cases, the prescribing information should be followed and maximum approved dose of anti-hyperglycemic agent should not be exceeded.

1. Additional monitoring outside of per protocol schedule (Table 9-1) is not needed if fasting glucose is less than 125 mg/dL (< 6.94 mmol/L).

2. If fasting glucose ≥ 125 mg/dL (≥ 6.94 mmol/L) and ≤ 160 mg/dL (≤ 8.88 mmol/L), patients will be asked to perform self-monitoring of blood glucose using finger stick blood testing (preferred choice) or urine dipstick testing (a urine dipstick can show a false-positive glucosuria in patients taking SGLT2 inhibitors). Initiation of anti-hyperglycemic therapy with metformin or anti-hyperglycemic agent of choice should be considered at this time, particularly for patients with symptoms of increased nausea, vomiting, decreased appetite, diarrhea, muscle cramps and fatigue. Tests should be performed at home QD for at least 2 weeks, taking note of time, fasted/fed state, and glucose levels in a monitoring log provided. Patients should bring this monitoring log to scheduled visits and review with treating physician. If patient observes at home 2 or more fasting blood glucose measurements > 160 mg/dL (> 8.88 mmol/L), and/or 2 or more random blood glucose measurements > 200 mg/dL (> 11.01 mmol/L) (or a combination of the 2), or 2 or more positive urine glucose testing before their next scheduled clinic visit, they should call their health care practitioner (HCP), inform the study site, and schedule a visit as soon as possible with the treating physician. Treatment with metformin or anti-hyperglycemic agent of choice should be started (See Figure 7-1).

3. If fasting blood glucose > 160 mg/dL (≥ 8.88 mmol/L) and < 250 mg/dL (≤ 13.87 mmol/L) on more than 2 occasions, start metformin or anti-hyperglycemic agent of choice. Patients should perform self-monitoring of blood glucose using finger stick blood testing or urine dipstick testing. Finger stick tests should be performed at home QD for at least 2 weeks, making note of time, fasted/fed state and glucose levels in a monitoring log provided. Patients should bring this monitoring log to scheduled visits and review with treating physician.

4. If fasting glucose ≥ 250 mg/dL (> 13.87 mmol/L), and the patient is not symptomatic, manage as for Step 3 above. If the patient is symptomatic, then hold CO-1686 and bring glucose under control acutely, if necessary using insulin with conversion to metformin or anti-hyperglycemic agent of choice once plasma glucose is controlled. Once patient is asymptomatic and deemed appropriate for additional therapy, CO-1686 may be re-introduced at a reduced dose, with concomitant metformin/anti-hyperglycemic agent of choice. Patients should perform self-monitoring of blood glucose using finger stick blood testing or urine dipstick testing. Finger stick tests should be performed at home BID for at least 2 weeks, before breakfast and before dinner, taking note of time, fasted/fed state and glucose levels in a monitoring log provided. Patients should bring this monitoring log to scheduled visits and review with treating physician.

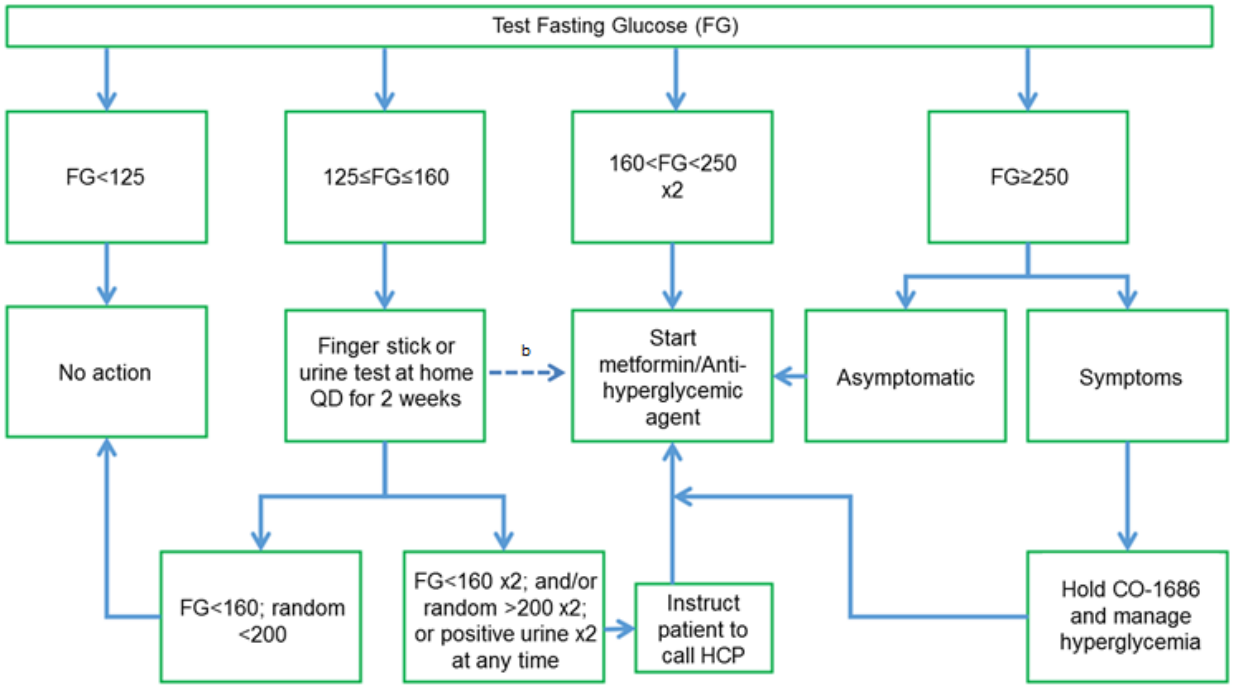
Metformin is contraindicated in patients with renal disease or renal dysfunction, among others, and use should follow the package insert and approved label. In order to minimize known gastrointestinal (GI) toxicity associated with metformin use, the extended release form and taking medication at bedtime are recommended to improve tolerability.[33] Additional recommendations to avoid GI toxicity with metformin include starting treatment at a reduced dose (500 mg QD) for 72 hours, increasing to 500 mg BID for 72 hours, and if necessary, and increasing up to 1,000 mg BID. If plasma glucose is not

adequately controlled with the regimen outlined above, then consider adding pioglitazone or a SGLT-2 inhibitor and consider consultation with an endocrinologist.

End-of-Treatment

When CO-1686 is discontinued, the need and use of anti-diabetic medications should be reassessed and the patient monitored and treated appropriately in order to minimize the possible hypoglycemia which may result.

Figure 7-1: Guidelines for Management of Hyperglycemia[a]



Abbreviations: FG = fasting plasma or serum glucose (in mg/dL).

[a] Guidelines intend to assist in managing patients that are non-diabetic at study start only.

[b] Consider initiation of anti-hyperglycemic therapy, particularly for patients with symptoms of increased nausea, vomiting, decreased appetite, diarrhea, muscle cramps and fatigue.

7.4.2 Erlotinib

Dose modifications for erlotinib are allowed in accordance with its prescribing information. Erlotinib will be withheld for:

- Acute onset of new or progressive unexplained pulmonary symptoms such as dyspnea, cough, and fever pending diagnostic evaluation for possible ILD
- CTCAE Grade 3 to 4 renal toxicity
- Total bilirubin levels > 3 x ULN or transaminases > 5 x ULN in patients without pre-existing hepatic impairment

- Total bilirubin > 2 x ULN or transaminases > 3 x ULN in patients with pre-existing hepatic impairment or biliary obstruction
- Persistent severe diarrhea not responsive to medical management
- Acute/worsening ocular disorders such as eye pain
- Severe rash not responsive to medical management
- Keratitis of Grade 3 to 4 or for Grade 2 lasting more than 2 weeks

Following interruption of erlotinib treatment for toxicity, once the event has resolved to baseline or Grade ≤ 1, erlotinib can be restarted with a 50 mg decrease with prospective sponsor approval.

Erlotinib will be discontinued if:

- ILD is confirmed
- Abnormal liver tests meeting the criteria for withholding drug as defined above do not improve to Grade 1 or baseline levels within 3 weeks
- Patient develops GI perforation
- Patient develops severe bullous, blistering, or exfoliating conditions
- Patient develops corneal perforation or severe ulceration
- A toxicity requiring erlotinib to be withheld does not improve or recurs on initiation of erlotinib

If the erlotinib dose is to be escalated or other agents are to be added in, the patient must be discontinued from the study, perform End-of-Treatment Visit procedures, and continue to the follow-up portion of the study.

7.5 Accountability of Protocol-specified Treatment

Study personnel will maintain accurate records of CO-1686 and erlotinib shipments/receipts, administration, and drug reconciliation. The study site is responsible for the return or destruction of CO-1686 and erlotinib as required. A drug management system will manage all sponsor-provided CO-1686 and erlotinib inventory at all sites. If erlotinib is procured and provided directly by the site, this inventory will be managed outside the drug management system. For sponsor provided protocol-specified treatment, the system will be required to manage study treatment requests and shipments.

Any CO-1686 and erlotinib accidentally or deliberately destroyed must be accounted for and documented. All bottles and blister packs must be accounted for prior to their destruction at the study center. Unused bottles and blister packs should be destroyed locally, with appropriate documentation provided. If destruction at the site is not possible, sponsor-provided supply should be returned to the drug depot as instructed by the sponsor. During the course of the study and at completion of the study, the number of bottles and blister packs of CO-1686 and erlotinib shipped, destroyed, provided to the patient, and returned must be reconciled.

7.6 Blinding/Masking of Treatment

The Phase 2 part of this study is open-label; the investigational product will not be blinded or masked. All patients enrolled will receive either PO CO-1686 or erlotinib. In the Phase 3 part of the study, the sponsor will be blinded to efficacy and safety results aggregated by randomized treatment group.

7.7 Treatment Compliance

Documentation of dosing will be recorded in a study specific patient diary provided by the sponsor (or designee). Study site personnel will enter the scheduled daily doses and the number of tablets to be taken each day. Dosing noncompliance is defined as a patient missing > 14 consecutive days of study medication in a 28-day visit window for 2 consecutive visits. Patients meeting noncompliance criteria will be required to discontinue study treatment. Study site personnel will review the dosing information with the patient (or legally authorized representative) on scheduled study visit days. Patients (or legally authorized representative) will be asked to record dosing information for CO-1686 or erlotinib taken at home in the patient diary and to bring the diary and all unused tablets with them to scheduled study visits. A compliance check and tablet count will be performed by study personnel. Study site personnel will record compliance information on the eCRF and retain the diary in the patient's medical record.

8 PRIOR AND CONCOMITANT THERAPIES

8.1 Treatment with CO-1686

Medications known to produce QT prolongation should be avoided during the study. If a drug that has the potential to cause QT prolongation is indicated to control AEs (e.g., $5HT_3$ inhibitor for nausea/vomiting), and the investigator believes that the patient is benefiting from CO-1686 therapy, then additional ECGs should be performed to monitor for potential QT_C changes. The use of such concomitant medications and an appropriate ECG monitoring plan should be agreed between the investigator and sponsor before starting administration of the concomitant medication.

All procedures performed and medications used during the study must be documented on the eCRF.

8.1.1 Anticancer or Experimental Therapy

No other anticancer therapies (including chemotherapy, radiation, hormonal treatment [except corticosteroids and megestrol acetate], antibody or other immunotherapy or other experimental drugs) of any kind will be permitted while the patient is participating in the study.

Palliative radiation therapy intended to provide relief of cancer-related symptoms is permitted while the patient is on study, as long as there is no evidence of disease progression per RECIST Version 1.1. Such palliative radiotherapy must be approved prospectively by the sponsor. Treatment should be held (not to exceed 14 consecutive days for 2 consecutive visits) while the patient is undergoing radiotherapy.

Additionally, a patient who continues treatment post-progression may undergo radiation or other procedures to specific lesions post-progression, if the patient continues to demonstrate overall benefit from treatment, and the sponsor agrees. See Section 5.1.2 for more details.

8.1.2 Hematopoietic Growth Factors and Blood Products

Erythropoietin, darbepoetin alfa, and/or hematopoietic colony-stimulating factors for treatment of cytopenias should be administered according to institutional guidelines. Prophylactic use of these agents is not permitted. Transfusion thresholds for blood product support will be in accordance with institutional guidelines.

8.1.3 CYP450 Isozyme Inhibitors and Inducers

In vitro studies suggested the potential involvement of CYP2C8 in CO-1686 metabolism and thus, clinically, there is potential for CO-1686 plasma concentrations to be increased in the presence of co-administered potent inhibitors of CYP2C8. CYP2D6 appears to play a minor role, but its involvement in CO-1686 metabolism cannot be fully ruled out. Therefore, caution should be exercised with strong inhibitors of CYP2C8 and CYP2D6. For example, CYP2C8 inhibitors such as gemfibrozil, trimethoprim, glitazones, montelukast, and quercetin and CYP2D6 inhibitors such as bupropion, fluoxetine, paroxetine, and quinidine should be avoided.

Inducers of CYP2C8 and CYP2D6 have the potential to decrease CO-1686 exposure. Therefore, caution should be exercised with rifampin, an inducer of CYP2C8. No inducers of CYP2D6 have been identified.

Regarding strong inhibitors or inducers of CYP2C8 and CYP2D6, selection of an alternative concomitant medication with no or minimal enzyme inhibition or induction potential is recommended.

Caution should be exercised in patients receiving CO-1686 and requiring concomitant medication with warfarin (Coumadin®; patients known to require concomitant therapy with anticoagulant therapy such as warfarin should have international normalized ratio (INR) monitored at screening and during the study), NSAIDs, or clopidogrel, as CO-1686 moderately inhibited CYP2C8, CYP2C9, and CYP2C19 activities *in vitro*.

A list of inhibitors and inducers of CYP2C8 and CYP2D6 to be avoided or used with caution in patients receiving CO-1686 is attached in Appendix C.

8.1.4 P-gp Substrates, Inhibitors and Inducers

Because CO-1686 is a P-gp inhibitor *in vitro*, caution should be exercised in patients receiving CO-1686 and requiring concomitant medication with digoxin, a P-gp substrate. Patients taking digoxin who are enrolled in the study are required to have digoxin levels monitored regularly via standard clinical practice.

CO-1686 is a P-gp substrate and thus, P-gp inhibitors have the potential to increase CO-1686 exposure. As such, caution should be exercised in patients receiving CO-1686 and the following P-gp inhibitors: amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir, ritonavir, quercetin, quinidine, ranolazine, and verapamil (see Appendix C).

Conversely, P-gp inducers have the potential to decrease CO-1686 exposure. Caution should be exercised in patients receiving CO-1686 and the following P-gp inducers: avasimibe, carbamazepine, phenytoin, rifampin, St John's wort, and tipranavir/ritonavir (see Appendix C).

8.1.5 Other Concomitant Medications

Therapies considered necessary for the patient's well-being may be given at the discretion of the investigator and should be documented on the eCRF. Other concomitant medications, except for analgesics, chronic treatments for concomitant medical conditions, or agents required for life-threatening medical problems, should be avoided.

Medications to consider for nausea that are not associated with QT prolongation include:

- Steroids (dexamethasone, methylprednisolone)
- Benzodiazepines
- Aprepitant
- Select anticholinergic agents (scopolamine)
- Trimethobenzamide
- Cannabinoids

Palonosetron is currently not listed on crediblemeds.org and a thorough QTc study showed no QTc effect. However, as rare cases of QTc prolongation have been reported, a more frequent ECG monitoring schedule should be adopted if used with CO-1686.

Because CO-1686 is absorbed optimally in an acidic environment, proton pump inhibitors or H_2 blockers should be used with caution. If gastric acid blockade is required, short acting antacids are preferred.

Herbal and complementary therapies should not be encouraged because of unknown side effects and potential drug interactions, but any taken by the patient should be documented appropriately on the eCRF.

8.2 Treatment with Erlotinib

Interactions between erlotinib and other medicinal products are described in the erlotinib prescribing information.[19]

9 STUDY PROCEDURES

Table 9-1 summarizes the procedures and assessments to be performed for all patients.

Table 9-2 summarizes the procedures and assessments to be performed in Phase 2 only for patients randomized to erlotinib, who progress on study, demonstrate T790M+ status at the screening biopsy, and agree to participate in the crossover component of the study to receive PO CO-1686 treatment.

All procedures and assessments are to be completed within ± 1 day of the scheduled time point and are synchronized with C1D1 of CO-1686 or erlotinib treatment unless otherwise noted.

With the introduction and following approval of this protocol amendment 3 version, crossover to CO-1686 after progression on erlotinib is no longer an option. All ongoing patients, will be treated on the Extension Phase of the study and should follow the schedule of assessments provided in Appendix D.

Table 9-1: Schedule of Assessments in Phase 2 (Before Crossover) and in Phase 3

Procedure[b]	Screening		Treatment Period (Daily Dosing)[a]							End-of-Treatment[t] 28 Days ±7 Days After Last Dose	Follow-up (Every 8 ± 1 weeks for scans, every 3 months ± 7 days for survival and subsequent therapy starting at End-of-Treatment)
	≤ 35 Days Prior to Cycle 1 Day 1	≤ 14 Days Prior to Cycle 1 Day 1	Cycle 1 Day 1 (C1D1)[c]	Cycle 1 Day 4 ± 1 Day[d]	Cycle 1 Day 8 ± 1 Day[d]	Cycle 1 Day 15 ± 1 Day[d]	Cycle 2 Day 1 (28 ± 3 days after C1D1)	Cycle 2 Day 15 ± 1 Day[d]	Cycle 3+ Every 28 ± 3 Days		
Informed consent	X										
Medical/oncology history	X										
Physical examination		X	X				X		X	X	
ECOG performance status		X	X				X		X	X	
Vital signs[e], height (screening only) and weight		X	X				X		X	X	
Prior/concomitant medications and procedures[f]	X		X				X		X	X	
Contraceptive counseling[g]	X									X	
Serum pregnancy test[h]		X								X	
Hematology, including reticulocytes[i]		X	X				X		X	X	
Fasting serum chemistry[j]		X	X	Fasting glucose only	Fasting glucose only	Fasting glucose only	X	Fasting glucose only	X	X	
Urinalysis[k]		X									

Table 9-1: Schedule of Assessments in Phase 2 (Before Crossover) and in Phase 3 *(Cont.)*

Procedure[b]	Screening		Treatment Period (Daily Dosing)[a]							End-of-Treatment[t] 28 Days ±7 Days After Last Dose	Follow-up (Every 8 ± 1 weeks for scans, every 3 months ± 7 days for survival and subsequent therapy starting at End-of-Treatment)
	≤ 35 Days Prior to Cycle 1 Day 1	≤ 14 Days Prior to Cycle 1 Day 1	Cycle 1 Day 1 (C1D1)[c]	Cycle 1 Day 4 ± 1 Day[d]	Cycle 1 Day 8 ± 1 Day[d]	Cycle 1 Day 15 ± 1 Day[d]	Cycle 2 Day 1 (28 ± 3 days after C1 D1)	Cycle 2 Day 15 ± 1 Day[d]	Cycle 3 + Every 28 ± 3 Days		
Tumor scans, including brain imaging (brain imaging at baseline and as clinically indicated)[l]	X								X (Every 8 ± 1 weeks from C3D1, etc.)	X	X
Tumor/metastasis biopsy (core or fine needle aspiration) for EGFR mutation assessment[m]	X									X (Optional Consent Required)	
Blood for biomarker/EGFR mutational testing and exploratory research[n]	X		X			X	X		X	X	
Blood for CYP evaluation (optional consent required)[o]			X								
Adverse events[p]	X	X	X				X		X	X	
CO-1686 or erlotinib dispensing/ administration			X				X		X		
Patient diary[q]							X		X	X	
Triplicate ECG assessments[r]		X	X		X	X	X		X	X	

Table 9-1: Schedule of Assessments in Phase 2 (Before Crossover) and in Phase 3 *(Cont.)*

Procedure[b]	Screening		Treatment Period (Daily Dosing)[a]							End-of-Treatment[t] 28 Days ±7 Days After Last Dose	Follow-up (Every 8 ± 1 weeks for scans, every 3 months ± 7 days for survival and subsequent therapy starting at End-of-Treatment)
	≤ 35 Days Prior to Cycle 1 Day 1	≤ 14 Days Prior to Cycle 1 Day 1	Cycle 1 Day 1 (C1D1)[c]	Cycle 1 Day 4 ± 1 Day[d]	Cycle 1 Day 8 ± 1 Day[d]	Cycle 1 Day 15 ± 1 Day[d]	Cycle 2 Day 1 (28 ± 3 days after C1 D1)	Cycle 2 Day 15 ± 1 Day[d]	Cycle 3 + Every 28 ± 3 Days		
Blood for sparse PK sampling and AAG serum levels (CO-1686 arm only)							X (Cycle 2 to 7 only)		X (Cycle 2 to 7 only)		
Quality of life Questionnaires[s]		X	X						X	X	
Survival status										X	X
Subsequent therapies for NSCLC										X	X

Abbreviations: AAG = alpha-1 acid glycoprotein; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ß-hCG = beta human chorionic gonadotropin; BUN = blood urea nitrogen; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; EORTC QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, Core 30; EORTC QLQ-LC13 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, Lung Cancer 13; MRI = magnetic resonance imaging; RECIST = Response Evaluation Criteria in Solid Tumors; WBC = white blood cells

[a] CO-1686 will be administered PO at 500 mg BID, with a meal or within 30 minutes after a meal and erlotinib will be administered PO QD at 150 mg on an empty stomach (1 hour before or 2 hours after ingesting food)

[b] Unless specified, procedure is completed ± 1 day of scheduled time point and is synchronized with C1D1 of CO-1686 or erlotinib.

[c] C1D1 and randomization can be the same day, but not required. C1D1 must be within 3 days of randomization. Procedures required on C1D1 may be omitted if completed ≤ 3 days earlier during the screening period.

[d] Fasting glucose required on C1D4 ± 1 day, C1D8 ± 1 day, C1D15 ± 1 day, and C2D15 ± 1 day for patients taking CO-1686 only. Not required for patients taking erlotinib.

[e] Vital signs (blood pressure, pulse, and temperature) taken predose on C1D1 and without reference to dose at every subsequent visit. All vital signs will be obtained after the patient has been resting for at least 5 min. Height is only required once at screening. Weight is measured at each visit.

[f] On C1D1 concomitant medications and procedures will be monitored pre- and postdose.

[g] Patients are to continue using double-barrier contraception for 12 weeks after last dose of CO-1686 and 2 weeks after the last dose of erlotinib and report any pregnancies during this period.

[h] Serum ß-hCG (evaluated by local labs) will be performed only on women of childbearing potential ≤ 3 days prior to C1D1 and at end-of-treatment. If the serum pregnancy test results are not available on Day 1, a urine pregnancy test can be performed on C1D1 to confirm that the patient is not pregnant prior to dosing.

Table 9-1: Schedule of Assessments in Phase 2 (Before Crossover) and in Phase 3 *(Cont.)*

Procedure[b]	Screening		Treatment Period (Daily Dosing)[a]							End-of-Treatment[t]	Follow-up (Every 8 ± 1 weeks for scans, every 3 months ± 7 days for survival and subsequent therapy starting at End-of-Treatment)
	≤ 35 Days Prior to Cycle 1 Day 1	≤ 14 Days Prior to Cycle 1 Day 1	Cycle 1 Day 1 (C1D1)[c]	Cycle 1 Day 4 ± 1 Day[d]	Cycle 1 Day 8 ± 1 Day[d]	Cycle 1 Day 15 ± 1 Day[d]	Cycle 2 Day 1 (28 ± 3 days after C1 D1)	Cycle 2 Day 15 ± 1 Day[d]	Cycle 3 + Every 28 ± 3 Days	28 Days ±7 Days After Last Dose	

[i] Includes hemoglobin, hematocrit, WBC and differential (with ANC), platelet count, and reticulocyte count ≤ 14 days prior to the first day of dosing (C1D1), on Day 1 for all subsequent cycles, and at end-of-treatment. Blood will be analyzed by a local laboratory to inform patient treatment decisions, and must be reviewed by the investigator prior to start of CO-1686 or erlotinib administration. Additional tests may be performed at the investigator's discretion.

[j] Includes total protein, albumin, creatinine, BUN or urea, total bilirubin, alkaline phosphatase, ALT, AST, ***fasting*** glucose, sodium, potassium, chloride, magnesium, CO_2, calcium, phosphorus, total cholesterol, HbA1c ≤ 14 days prior to first day of dosing (C1D1), on Day 1 for all subsequent cycles, and at end-of-treatment. Samples will be analyzed by a local laboratory. Fast is defined as 8 hour fast (no food or liquid other than water). HbA1c will be measured every other visit (Cycles 3, 5, 7, etc.) after initiating study drug. Fasting glucose at C1D4, C1D8, C1D15, and C2D15 is only required for patients randomized to CO-1686.

[k] Includes dipstick for protein, glucose, blood, pH, and ketones ≤ 14 days prior to first day of dosing (C1D1). Samples will be analyzed by a local laboratory. If dipstick findings are abnormal, then a microscopic evaluation will be performed to assess the abnormal findings.

[l] Tumor scans obtained within 35 days prior to C1D1, may be used as the baseline scans. Scans will include the chest and abdomen (preferably CT scans with appropriate slice thickness per RECIST Version 1.1), using the same methods throughout the study that were used to detect lesions at baseline. Scans of the pelvis (CT or MRI) are required if there is prior evidence of local disease or if clinically indicated (symptomatic patients). Other studies (MRI, X-ray) may be performed if required. Brain imaging (CT/MRI) is required at baseline. Patients with brain lesions detected at baseline will not be eligible for the study. Brain imaging is not required on study unless clinically indicated. Tumor scans will be performed during screening, every 8 ± 1 weeks thereafter (Day 1 of Cycles 3, 5, 7, etc.) until tumor progression, and at the end-of-treatment. Tumor scans do not need to be repeated at end-of-treatment if < 2 weeks since last scan or the patient had disease progression at the last scan. Patients who discontinue treatment without progression should continue to be scanned according to the protocol until disease progression occurs. Patients who continue treatment with CO-1686 or erlotinib post-progression should continue to be scanned according to the protocol until they discontinue from the study. An MRI may be used in place of a CT at end-of-treatment scan if required per local authorities. Scans will be evaluated locally for patient treatment decisions. Copies of tumor scans will be collected centrally to facilitate independent evaluation if subsequently required.

[m] Biopsy (core or fine needle aspiration) of either primary or metastatic tissue to determine EGFR mutation status and for the development of a validated tissue-based EGFR T790M test. If a biopsy was performed within 60 days of C1D1, and no intervening treatment was given, a repeat biopsy is not required if adequate tumor tissue can be provided. At progression and/or end-of-treatment, a tumor biopsy will performed if the patient provides additional consent at this time. All tumor tissue will be processed locally as formalin-fixed paraffin-embedded (FFPE) tissue. Exploratory biomarker analysis will be done if FFPE tissue is available after EGFR mutation status and diagnostic test validation.

[n] Blood sampling for biomarker/EGFR mutational testing and exploratory research will be collected at screening (prior to biopsy, where possible); predose on C1D1, C1D15, then at every study Cycle visit Day 1 (every 28 ± 3 days), and at the End-of-Treatment Visit.

[o] Blood for CYP evaluation to be collected predose on Day 1 (Cycle 1) for patients randomized to receive CO-1686 who have signed optional consent.

Table 9-1: Schedule of Assessments in Phase 2 (Before Crossover) and in Phase 3 *(Cont.)*

Procedure[b]	Screening		Treatment Period (Daily Dosing)[a]							End-of-Treatment[t] 28 Days ±7 Days After Last Dose	Follow-up (Every 8 ± 1 weeks for scans, every 3 months ± 7 days for survival and subsequent therapy starting at End-of-Treatment)
	≤ 35 Days Prior to Cycle 1 Day 1	≤ 14 Days Prior to Cycle 1 Day 1	Cycle 1 Day 1 (C1D1)[c]	Cycle 1 Day 4 ± 1 Day[d]	Cycle 1 Day 8 ± 1 Day[d]	Cycle 1 Day 15 ± 1 Day[d]	Cycle 2 Day 1 (28 ± 3 days after C1 D1)	Cycle 2 Day 15 ± 1 Day[d]	Cycle 3 + Every 28 ± 3 Days		

[p] Patients will be monitored for AEs from the time the first dose of CO-1686 or erlotinib is administered through 28 days after the last dose (ongoing SAEs at the time of the End-of-Treatment Visit will be followed until resolution or stabilization). Study procedure-related AEs that occur after signing of the ICF and before administration of CO-1686 or erlotinib will also be collected. On C1D1 AEs will be monitored pre- and postdose.

[q] Patient diaries should be collected and reviewed for compliance.

[r] Taken in triplicate as 10 second tracings > 2 min apart anytime during screening, 5 to10 minutes prior to dosing on C1D1, C1D8, C1D15, then at every study cycle visit during treatment (occurring at 28 ± 3 days intervals) and at end-of-treatment, any time after treatment is discontinued.

[s] QOL questionnaires (EORTC QLQ-C30, EORTC QLQ-LC13, the DLQI, and the EQ-5D) will be collected at screening, predose on C1D1 then every 8 ± 1 weeks for the first 6 months (Day 1 of Cycles 3, 5, 7, inclusive). After Cycle 7, questionnaires will be collected every 12 ± 1 weeks (Day 1 of Cycles 10, 13, 16, etc.) and at end-of-treatment.

[t] In the Phase 2 part only, patients participating in the crossover portion of the study should only have End-of-Treatment Visit once, after completing crossover study treatment. However, if patient deemed not eligible for crossover, assessments done for crossover eligibility can be used for end-of-treatment assessments.

Table 9-2: Phase 2 Part Only - Schedule of Assessments on Crossover to Oral CO-1686 Treatment Following Progression on Erlotinib

Procedure[b]	Crossover Assessments[Δ]	Treatment Period (Daily Dosing)[a]							End-of-Treatment	Follow-up (every 8 ± 1 weeks for scans, every 3 months ± 7 days for survival and subsequent therapy, starting at End-of-Treatment)
	≤ 35 Days from Radiographic Progression on Erlotinib	XO-Cycle 1 Day 1 (C1D1)[c]	XO-Cycle 1 Day 4 ± 1 Day[d]	XO-Cycle 1 Day 8 ± 1 Day[d]	XO-Cycle 1 Day 15 ± 1 Day[d]	XO-Cycle 2 Day 1 (28 ± 3 days after C1D1)	XO-Cycle 2 Day 15 ± 1 Day[d]	XO-Cycle 3 + Every 28 ± 3 Days		
Informed consent	X									
Physical examination	X	X				X		X	X	
ECOG performance status	X	X				X		X	X	
Vital signs[e] and weight	X	X				X		X	X	
Prior/concomitant medications and procedures[f]	X	X				X		X	X	
Contraceptive counseling[g]	X								X	
Serum pregnancy test[h]	X								X	
Hematology, including reticulocytes[i]	X	X				X		X	X	
Fasting serum chemistry[j]	X	X	Fasting glucose only	Fasting glucose only	Fasting glucose only	X	Fasting glucose only	X	X	
Urinalysis[k]	X									
Tumor scans[l]	X							X (Every 8 ±1 weeks from C3D1, etc.)	X	X
Tumor/metastasis biopsy for T790M mutation[m]	X								X (Optional consent required)	

Table 9-2: Phase 2 Part Only - Schedule of Assessments on Crossover to Oral CO-1686 Treatment Following Progression on Erlotinib *(Cont.)*

Procedure[b]	Crossover Assessments[Δ]	Treatment Period (Daily Dosing)[a]							End-of-Treatment	Follow-up (every 8 ± 1 weeks for scans, every 3 months ± 7 days for survival and subsequent therapy, starting at End-of-Treatment)
	≤ 35 Days from Radiographic Progression on Erlotinib	XO-Cycle 1 Day 1 (C1D1)[c]	XO-Cycle 1 Day 4 ± 1 Day[d]	XO-Cycle 1 Day 8 ± 1 Day[d]	XO-Cycle 1 Day 15 ± 1 Day[d]	XO-Cycle 2 Day 1 (28 ± 3 days after C1 D1)	XO-Cycle 2 Day 15 ± 1 Day[d]	XO-Cycle 3 + Every 28 ± 3 Days		
Blood for biomarker/EGFR mutational testing and exploratory research[n]	X	X			X	X		X	X	
Blood for CYP evaluation (optional consent required)[o]		X								
Adverse events[p]	X	X				X		X	X	
CO-1686 dispensing/administration		X				X		X		
Patient diary[q]		X				X		X	X	
Triplicate ECG assessments[r]	X	X		X	X	X		X	X	
Blood for sparse PK sampling and AAG serum levels						X (Cycle 2 to 7 only)		X (Cycle 2 to 7 only)		
Quality of life questionnaires[s]	X	X						X	X	
Survival status									X	X
Subsequent therapies for NSCLC									X	X

Table 9-2: Phase 2 Part Only - Schedule of Assessments on Crossover to Oral CO-1686 Treatment Following Progression on Erlotinib *(Cont.)*

Procedure[b]	Crossover Assessments[Δ]	Treatment Period (Daily Dosing)[a]								
	≤ 35 Days from Radiographic Progression on Erlotinib	XO-Cycle 1 Day 1 (C1D1)[c]	XO-Cycle 1 Day 4 ± 1 Day[d]	XO-Cycle 1 Day 8 ± 1 Day[d]	XO-Cycle 1 Day 15 ± 1 Day[d]	XO-Cycle 2 Day 1 (28 ± 3 days after C1 D1)	XO-Cycle 2 Day 15 ± 1 Day[d]	XO-Cycle 3 + Every 28 ± 3 Days	End-of-Treatment	Follow-up (every 8 ± 1 weeks for scans, every 3 months ± 7 days for survival and subsequent therapy, starting at End-of-Treatment)

Abbreviations: AAG = alpha-1 acid glycoprotein; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ; ß-hCG = beta human chorionic gonadotropin; BUN = blood urea nitrogen; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; EORTC QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, Core 30; EORTC QLQ-LC13 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, Lung Cancer 13; MRI = magnetic resonance imaging; RECIST = Response Evaluation Criteria in Solid Tumors; WBC = white blood cells

Δ Crossover assessments to determine eligibility should be completed within 35 days of radiographic progression on erlotinib.

[a] CO-1686 will be administered at 500 mg BID, with a meal or within 30 minutes after a meal.

[b] Unless specified, procedure is completed ± 1 day of scheduled time point and is synchronized with XO-C1D1 of CO-1686.

[c] Procedures required on XO-C1D1 may be omitted if completed ≤ 3 days earlier during the XO-screening period.

[d] Fasting glucose required on XO-C1D4 ± 1 day, XO-C1D8 ± 1 day, XO-C1D15 ± 1 day, XO-C2D15 ± 1 day.

[e] Vital signs (blood pressure, pulse, and temperature) taken predose on XO-C1D1 and without reference to dose at every subsequent visit. All vital signs will be obtained after the patient has been resting for at least 5 min. Weight is measured at each visit.

[f] On C1D1 concomitant medications and procedures will be monitored pre- and postdose.

[g] Patients are to continue using adequate contraception for 12 weeks after last dose of CO-1686.

[h] Serum ß-hCG (evaluated by local labs) will be performed only on women of childbearing potential ≤ 3 days prior to enrollment in XO and at end-of-treatment. If the serum pregnancy test results are not available prior to enrollment in XO, a urine pregnancy test can be performed at enrollment in XO to confirm that the patient is not pregnant prior to dosing.

[i] Includes hemoglobin, hematocrit, WBC and differential (with ANC), platelet count, and reticulocyte count ≤ 14 days prior to the first day of dosing (XO-C1D1), on Day 1 for all subsequent XO-Cycles, and at end-of-treatment. Blood will be analyzed by a local laboratory to inform patient treatment decisions, and must be reviewed by the investigator prior to start of CO-1686 administration. Additional tests may be performed at the investigator's discretion.

[j] Includes total protein, albumin, creatinine, BUN or urea, total bilirubin, alkaline phosphatase, ALT, AST, ***fasting*** glucose, sodium, potassium, chloride, magnesium, CO_2, calcium, phosphorus, total cholesterol, HbA1c ≤ 14 days prior to first day of dosing (XO-C1D1), on Day 1 for all subsequent XO-Cycles, and at end-of-treatment. Samples will be analyzed by a local laboratory. Fast is defined as 8 hour fast (no food or liquid other than water). HbA1c will be measured every other visit (XO-Cycles 3, 5, 7, etc.) after initiating study drug.

[k] Includes dipstick for protein, glucose, blood, pH, and ketones. Samples will be analyzed by a local laboratory. If dipstick findings are abnormal, then a microscopic evaluation will be performed to assess the abnormal findings.

Table 9-2: Phase 2 Part Only - Schedule of Assessments on Crossover to Oral CO-1686 Treatment Following Progression on Erlotinib *(Cont.)*

Procedure[b]	Crossover Assessments[Δ]	Treatment Period (Daily Dosing)[a]								
	≤ 35 Days from Radiographic Progression on Erlotinib	XO-Cycle 1 Day 1 (C1D1)[c]	XO-Cycle 1 Day 4 ± 1 Day[d]	XO-Cycle 1 Day 8 ± 1 Day[d]	XO-Cycle 1 Day 15 ± 1 Day[d]	XO-Cycle 2 Day 1 (28 ± 3 days after C1 D1)	XO-Cycle 2 Day 15 ± 1 Day[d]	XO-Cycle 3 + Every 28 ± 3 Days	End-of-Treatment	Follow-up (every 8 ± 1 weeks for scans, every 3 months ± 7 days for survival and subsequent therapy, starting at End-of-Treatment)

[l] Tumor scans showing radiographic progression on erlotinib should be used as the crossover assessment scans. Brain imaging is not required on study unless clinically indicated. Tumor Scans will be performed every 8 ± 1 weeks after starting CO-1686 (Day 1 of XO-Cycles 3, 5, 7, etc.) until tumor progression, and at the end-of-treatment. Tumor scans do not need to be repeated at end-of-treatment if < 2 weeks since last scan or the patient had disease progression at the last scan. An MRI may be used in place of a CT at End-of-Treatment scan if required per local authorities. Patients who discontinue treatment without progression should continue to be scanned according to the protocol until disease progression occurs. Scans will be evaluated locally for patient treatment decisions. Copies of tumor scans will be collected centrally to facilitate independent evaluation if subsequently required.

[m] Biopsy (core or fine needle aspiration) of either primary or metastatic tissue to determine presence of T790M. Tissue material must be obtained within 35 days of XO-Cycle 1. At progression and/or end-of-treatment, a tumor biopsy will performed if the patients provides additional consent at this time. All tumor tissue will be processed locally as formalin-fixed paraffin-embedded (FFPE) tissue. Exploratory biomarker analysis will be done if FFPE tissue is available after EGFR mutation status and diagnostic test validation.

[n] Blood sampling for biomarker/EGFR mutational testing and exploratory research will be collected at XO-screening (prior to biopsy, where possible); predose on XO-C1D1, at Cycle 1 Day 15, then at every study XO-Cycle visit (every 28 ± 3 days), and at the End-of-Treatment Visit.

[o] Blood for CYP evaluation to be collected predose on Day 1 (Cycle 1) for patients randomized to receive CO-1686 who have signed optional consent.

[p] AEs will be collected from the signing of the ICF for crossover through 28 days after the last dose of CO-1686. On XO-C1D1 AEs will be monitored pre- and postdose.

[q] Patient diaries should be collected and reviewed for compliance. If not completed previously, diary from final dose of erlotinib should be reviewed during the crossover assessment period.

[r] Taken in triplicate as 10 second tracings > 2 min apart anytime during screening, 5 to 10 minutes prior to dosing on Day 1 (XO-Cycle 1), XO-C1D8, XO-C1D15, then at every study XO-cycle visit during treatment (occurring at 28 ± 3 days intervals) and at end-of-treatment, any time after treatment is discontinued.

[s] QOL questionnaires (EORTC QLQ-C30, EORTC QLQ-LC13, the DLQI, and the EQ-5D) will be collected at screening, predose on Day 1 (XO-Cycle 1), then every 8 ± 1 weeks for the first 6 months (Day 1 of XO-Cycles 3, 5, 7, etc.). After XO-Cycle 7, questionnaires will be collected every 12 ± 1 weeks (Day 1 of XO-Cycles 10, 13, 16, etc.) and at end-of-treatment.

9.1 Screening Period

Following written informed consent, and unless otherwise specified, the following assessments should be performed during the 35-day period prior to the first dose of study treatment. Obtaining written informed consent does not signify the start of the screening period. The first screening activity performed after signature of the ICF begins the 35-day screening period. If a biopsy was performed within 60 days of C1D1, and no intervening treatment was given, a repeat biopsy is not required if adequate tumor tissue can be provided for mutational analysis and biomarker research. Assessments performed prior to patient signing informed consent are acceptable only if confirmed to have been standard of care. Unless otherwise specified, if a procedure is completed more than 35 days prior to the first day of dosing it will need to repeated prior to C1D1. C1D1 and randomization can be the same day, but are not required to be the same day. C1D1 must occur within 3 days after date of randomization.

To be performed **≤ 60 days prior to Cycle 1 Day 1:**

- Biopsy (core or fine needle aspiration [FNA]) or surgical resection of primary or metastatic lesions ≤ 60 days of C1D1. To ensure adequate viable tumor tissue is obtained, image-guided biopsies should be achieved with 18- to 20-gauge cutting needles to provide 1 to 3 cores measuring 1 to 1.5 cm in length.

To be performed **≤ 35 days prior to Cycle 1 Day 1:**

- Documented evidence of a tumor with an EGFR mutation known to be associated with CO-1686 drug sensitivity (exon 19 deletion, L858R, G719X, L861Q, S768I, etc.) as determined by testing of the NSCLC tumor using an approved laboratory technique
- Medical history, including demographic information (birth date, race, gender, etc.) smoking status, and oncology history including date of NSCLC diagnosis, prior cancer treatment, and any surgical procedures
- Prior and concomitant medications and procedures. Details of medications taken within 28 days of C1D1 should be recorded
- Contraceptive counseling
- Study procedure-related AEs
- Tumor assessments of the chest and abdomen. Assessments should consist of clinical examination and appropriate imaging techniques (CT scans with appropriate slice thickness per RECIST Version 1.1); scans of the pelvis (CT or MRI) are required if there is prior evidence of local disease or if clinically indicated (symptomatic patients). Other studies (MRI and X-ray) may be performed if required. The same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study.
- Brain imaging (CT/MRI) is required at baseline. Patients with brain lesions detected at baseline are excluded from the study.
- Blood sampling for biomarker/EGFR mutational testing and exploratory research that may lead to development of a blood-based EGFR test. This should be collected prior to the biopsy where possible. Detailed sample handling instructions are provided in the Laboratory Manual.

To be performed **≤ 14 days prior to Cycle 1 Day 1:**

- Physical examination by body system
- ECOG performance status
- Vital signs (blood pressure, pulse, and temperature), height, and weight
- Hematology (hemoglobin, hematocrit, WBC and differential [with ANC], platelet count, and reticulocyte count) ≤ 14 days prior to the first day of dosing (C1D1)
- ***Fasting*** serum chemistry (total protein, albumin, creatinine, blood urea nitrogen [BUN] or urea, total bilirubin, alkaline phosphatase, ALT, AST, fasting glucose, sodium, potassium, magnesium, chloride, bicarbonate [CO_2], calcium, phosphorus, total cholesterol and hemoglobin A1c [HbA1c]) ≤ 14 days prior to the first day of dosing (C1D1)
- Urinalysis performed on freshly voided clean sample (dipstick for protein, glucose, blood, pH, and ketones) ≤ 14 days prior to C1D1. If dipstick findings are abnormal based on investigator judgment, then a microscopic evaluation will be performed to assess the abnormal findings
- Study procedure-related AEs
- 12-lead ECG (in triplicate, 10-sec tracings > 2 min apart)
- QOL questionnaires (EORTC QLQ-C30, EORTC QLQ-LC13, the DLQI, and the EQ-5D)

To be performed **≤ 3 days prior to Cycle 1 Day 1:**

- Serum pregnancy test (by local laboratory) ≤ 3 days prior to C1D1 for women of childbearing potential. If the serum pregnancy test results are not available on Day 1, a urine pregnancy test can be performed on C1D1 to confirm that the patient is not pregnant prior to dosing. Both values should be entered in the eCRF.

At the end of screening, patients will be randomized to treatment with CO-1686 or erlotinib (see Section 7.2).

9.2 Treatment Period

Before enrolling a patient, all eligibility criteria must be satisfied.

Patients will take CO-1686 or erlotinib, as directed.

CO-1686 should be taken with 8 oz (240 mL) of water and with a meal or within 30 minutes after a meal.

Erlotinib should be taken with 8 oz of water on an empty stomach; i.e., at least 1 hour before or 2 hours after the ingestion of food.

Patients will record the dose and timing of administration of PO CO-1686 or erlotinib in their daily dosing diary.

Unless otherwise specified, all patients will undergo the following procedures and assessments.

9.2.1 Cycle 1 Day 1 (C1D1)

Patients will be required to take their first dose of CO-1686 or erlotinib at the study site. The following procedures will be performed predose and postdose, and the patient diary will be provided to the patient for information to be collected and reviewed during each visit. Procedures required on C1D1 may be omitted if completed ≤ 3 days earlier during the screening period.

Predose Assessments	Postdose Assessments
• Physical examination • ECOG performance status • Vital signs (blood pressure, pulse, and temperature) • Weight • Concomitant medications and procedures since Screening visit • Hematology (including reticulocyte count) and ***fasting*** serum chemistry (includes ***fasting*** glucose). • Blood sampling for biomarker/EGFR mutational testing and exploratory research • Blood sampling for CYP testing (requires optional consent – CO-1686 only) • Study procedure-related AEs experienced by the patient between signing the ICF and before the first dose of study treatment • CO-1686 tablets or erlotinib tablets will be dispensed to the patient along with patient diary • 12-lead ECG (in triplicate, 10-sec tracings > 2 min apart) 5 to10 mins prior to dosing • QOL questionnaires (EORTC QLQ-C30, EORTC QLQ-LC13, the DLQI, and the EQ-5D)	• AEs experienced by the patient since dosing will be documented • Concomitant medications administered and procedures completed since dosing will be recorded

9.2.2 Cycle 1 Day 4 (± 1 Day)

The following procedure will be performed at C1 Day 4 (± 1 day):

- ***Fasting*** glucose **(CO-1686 treatment arm only)**

9.2.3 Cycle 1 Day 8 (± 1 Day)

The following procedures will be performed at C1 Day 8 (± 1 day):

- ***Fasting*** glucose **(CO-1686 treatment arm only)**
- 12-lead ECG (in triplicate, 10-sec tracings > 2 min apart) 5 to 10 mins prior to dosing **(both treatment arms)**

9.2.4 Cycle 1 Day 15 (± 1 Day)

The following procedures will be performed at C1D15 (± 1 day):

- ***Fasting*** glucose **(CO-1686 treatment arm only)**
- Blood sampling for biomarker/EGFR mutational testing and exploratory research **(both treatment arms)**
- 12-lead ECG (in triplicate, 10-sec tracings > 2 min apart) 5 to 10 mins prior to dosing **(both treatment arms)**

9.2.5 Cycle 2 Day 15 (± 1 Day)

The following procedure will be performed at C1D15 (± 1 day):

- ***Fasting*** glucose **(CO-1686 treatment arm only)**

9.2.6 Cycle 2 Day 1 (Occurring 28 ± 3 Days After C1D1) and Cycle 3 + Day 1 (Every 28 ± 3 Days Thereafter)

The following procedures will be performed at 28 ± 3 day intervals:

- Physical examination
- ECOG performance status
- Vital signs (blood pressure, pulse, and temperature)
- Weight
- 12-lead ECG (in triplicate, 10-sec tracings > 2 min apart) 5 to 10 mins prior to dosing
- Hematology (including reticulocyte count) and ***fasting*** serum chemistry (includes ***fasting*** glucose). HbA1c will be measured every other visit (Cycles 3, 5, 7, etc.).
- Blood sampling for biomarker/EGFR mutational testing and exploratory research
- Serum alpha-1 acid glycoprotein (AAG) samples and PK blood sample prior to dose (Day 1 of Cycles 2 to 7 only, Section 9.6.3) (CO-1686 treatment arm only) for central laboratory analysis. Blood draw time relative to the last dosing time will be recorded
- Concomitant medications and procedures since last visit
- AE monitoring
- Collection and review of patient diary
- QOL questionnaires (EORTC QLQ-C30, EORTC QLQ-LC13, the DLQI, and the EQ-5D) – at 8 ± 1 weeks for 6 months (Day 1 of Cycles 3, 5, 7 inclusive). After Cycle 7 visit, questionnaires will be collected every 12 ± 1 weeks (Day 1 of Cycles 10, 13, 16, etc.)
- CO-1686 tablets or erlotinib tablets will be dispensed to the patient and a new patient diary provided
- Tumor assessments will be performed every 8 ± 1 weeks (Day 1 of Cycles 3, 5, 7, etc.) after dosing until tumor progression

9.3 Phase 2 Part Only: Crossover to CO-1686 Treatment After Progression on Erlotinib

Patients initially randomized to erlotinib may participate in a crossover phase to receive CO-1686 if eligible. To be eligibile for the crossover phase patients must meet all the following inclusion criteria:

- Demonstrate presence of the T790M mutation after radiographic progression on erlotinib
- Exhibit adequate hematological and biological function as described in Inclusion Criterion #8

In addition, patients will be excluded from crossover if:

- Patient must take medications that are known to prolong QTc interval as described in Exclusion Criterion #7

  OR

- Patient exhibits cardiac abnormalities or history as described in Exclusion Criterion #9

The sponsor must approve all patients for crossover eligibility. Patients eligible for crossover portion of the study will receive CO-1686 treatment and will be monitored for efficacy and safety during this period as outlined in Table 9-2. Tissue and blood specimens will be used to explore biomarkers that may be predictive of response or primary resistance to CO-1686.

9.3.1 Crossover Assessment (XO-assessment)

The following baseline assessments will be established prior to the first dose of PO CO-1686 and ≤ 35 days following radiographic progression on erlotinib. Patient will be required to sign Crossover ICF before screening procedures begin. Scans used to determine radiographic progression on erlotinib will be used as baseline scans in crossover:

- Physical examination
- ECOG performance status
- Vital signs (blood pressure, pulse, and temperature)
- Weight
- Concomitant medications and procedures
- Contraceptive counseling
- Serum pregnancy test (by local laboratory) ≤ 3 days prior to XO-C1D1 for women of childbearing potential. If the serum pregnancy test results are not available on XO-C1D1, a urine pregnancy test can be performed on XO-C1D1 to confirm that the patient is not pregnant prior to dosing. Both values should be entered in the eCRF.
- Hematology (including reticulocyte count), and ***fasting*** serum chemistry (including HbA1c and a ***fasting*** glucose measurement): Must meet Inclusion Criterion #8
- Urinalysis performed on freshly voided clean sample (dipstick for protein, glucose, blood, pH, and ketones). If dipstick findings are abnormal based on investigator judgment, then a microscopic evaluation will be performed to assess the abnormal findings.
- Biopsy (core or FNA) of primary or metastatic tissue to determine EGFR mutation status for crossover eligibility, assessed by a local or central laboratory: MUST BE T790M +

- AE monitoring
- Blood sampling for biomarker/EGFR mutational testing exploratory research
- 12-lead ECG (in triplicate, 10-sec tracings > 2 min apart)
- QOL Questionnaires (EORTC QLQ-C30, EORTC QLQ-LC13, the DLQI, and the EQ-5D)
- Collection and review of final patient diary from erlotinib treatment, if not already collected and reviewed

To be performed **≤ 3 days prior to enrollment:**

- Serum pregnancy test (by local laboratory) ≤ 3 days prior to enrollment for women of childbearing potential. If the serum pregnancy test results are not available at enrollment, a urine pregnancy test can be performed at enrollment to confirm that the patient is not pregnant prior to dosing. Both values should be entered in the eCRF.

9.3.2 Crossover Treatment Period

9.3.2.1 Crossover Cycle 1 Day 1 (XO-C1D1)

Patients will be required to take their first dose of CO-1686 at the study site. The following procedures will be performed predose and postdose, and the patient diary information will be collected and reviewed during the visit. Procedures required on XO-C1D1 may be omitted if completed ≤ 3 days earlier during the XO-screening period.

Predose Assessments	Postdose Assessments
• Physical examination • ECOG performance status • Vital signs (blood pressure, pulse, and temperature) • Weight • Concomitant medications and procedures • Hematology (including reticulocyte count) and fasting serum chemistry • Blood sampling for biomarker/EGFR mutational testing exploratory research • Blood sampling for CYP testing (requires optional consent) • AE monitoring • CO-1686 tablets will be dispensed to the patient and new patient diary provided • 12-lead ECG (in triplicate, 10-sec tracings > 2 min apart) 5 to10 mins prior to dosing • QOL questionnaires (EORTC QLQ-C30, EORTC QLQ-LC13, the DLQI, and the EQ-5D)	• AEs experienced by the patient since dosing will be documented • Concomitant medications administered since dosing will be recorded

9.3.2.2 Crossover Cycle 1 Day 4 (± 1 Day) (XO-C1D4)

The following procedure will be performed at Crossover C1 Day 4 (± 1 day):

- ***Fasting*** glucose

9.3.2.3 Crossover Cycle 1 Day 8 (± 1 Day) (XO-C1D8)

The following procedures will be performed at Crossover C1 Day 8 (± 1 day):

- ***Fasting*** glucose
- 12-lead ECG (in triplicate, 10-sec tracings > 2 min apart) 5 to 10 mins prior to dosing

9.3.2.4 Crossover Cycle 1 Day 15 (± 1 Day) (XO-C1D15)

The following procedures will be performed at Crossover C1D15 (± 1 day):

- ***Fasting*** glucose
- 12-lead ECG (in triplicate, 10-sec tracings > 2 min apart) 5 to 10 mins prior to dosing
- Blood sampling for biomarker/EGFR mutational testing and exploratory research

9.3.2.5 Crossover Cycle 2 Day 1 (Occurring 28 ± 3 Days After XO-C1D1)

The following procedures will be performed at 28 ± 3 day intervals:

- Physical examination
- ECOG performance status
- Vital signs (blood pressure, pulse, and temperature)
- Weight
- 12-lead ECG (in triplicate, 10-sec tracings > 2 min apart) 5 to 10 mins prior to dosing
- Hematology (including reticulocyte count) and ***fasting*** serum chemistry (includes ***fasting*** glucose). HbA1c will be measured every other visit (XO-Cycles 3, 5, 7, etc.), after initiating CO-1686.
- Blood sampling for biomarker/EGFR mutational testing and exploratory research
- Serum AAG samples and PK blood sample prior to dose (Day 1 of XO-Cycles 2 to 7 only, Section 9.6.3; Table 9-2) for central laboratory analysis. Blood draw time relative to the last dosing time will be recorded
- Concomitant medications and procedures since last visit
- AE monitoring
- Collection and review of patient diary
- CO-1686 tablets will be dispensed to the patient and a new patient diary provided

9.3.2.6 Crossover Cycle 2 Day 15 (± 1 Day) (XO-C2D15)

The following procedure will be performed at Crossover C2D15 (± 1 day):

- ***Fasting*** glucose

9.3.2.7 Crossover Cycle 3 + Day 1 (Every 28 ± 3 Days Thereafter)

The following procedures will be performed at 28 ± 3 day intervals:

- Physical examination
- ECOG performance status
- Vital signs (blood pressure, pulse, and temperature)
- Weight
- 12-lead ECG (in triplicate, 10-sec tracings > 2 min apart) 5 to 10 mins prior to dosing
- Hematology (including reticulocyte count) and ***fasting*** serum chemistry (includes ***fasting*** glucose). HbA1c will be measured every other visit (XO-Cycles 3, 5, 7, etc.), after initiating CO-1686.
- Blood sampling for biomarker/EGFR mutational testing and exploratory research
- Serum AAG samples and PK blood sample prior to dose (Day 1 of XO-Cycles 2 to 7 only, Section 9.6.3; Table 9-2) for central laboratory analysis. Blood draw time relative to the last dosing time will be recorded
- Concomitant medications and procedures since last visit
- AE monitoring
- Collection and review of patient diary
- QOL questionnaires (EORTC QLQ-C30, EORTC QLQ-LC13, the DLQI, and the EQ-5D) – at 8 ± 1 weeks for 6 months (Day 1 of Crossover Cycles 3, 5, 7, inclusive). After Crossover Cycle 7 visit, questionnaires will be collected every 12 weeks (Day 1 of Cycles 10, 13, 16, etc.) and at end-of-treatment
- CO-1686 tablets will be dispensed to the patient and a new patient diary provided
- Tumor assessments will be performed every 8 ± 1 weeks (Day 1 of XO Cycles 3, 5, 7, etc.) after dosing until tumor progression

9.4 End-of-Treatment Visit

The following procedures will be performed for all patients 28 days (± 7 days) after the last dose of protocol-specified treatment (initial study treatment or crossover treatment, whichever comes last).

- Physical examination
- ECOG performance status
- Vital signs (blood pressure, pulse, and temperature)
- Weight
- Concomitant medications and procedures since last visit
- Contraceptive counseling
- Serum pregnancy test for women of childbearing potential
- Hematology (including reticulocyte count), and ***fasting*** serum chemistry (includes ***fasting*** glucose)
- Tumor scans (using the same methodology as was used at screening) unless it has been < 2 weeks since last scan or disease progression was noted on the last scan. An MRI may be used in place of a CT at end-of-treatment scan if required per local authorities.
- Optional tumor biopsy (core or FNA; **requires additional consent**)

- Blood sampling for biomarker/EGFR mutational testing and exploratory research
- AE monitoring (until 28 days after last dose of protocol-specified treatment; then only ongoing SAEs are followed until resolution or stabilization)
- Collection and review of patient diary
- 12-lead ECG (in triplicate, 10-sec tracings > 2 min apart)
- QOL questionnaires (EORTC QLQ-C30, EORTC QLQ-LC13, the DLQI, and the EQ-5D)
- Survival status
- Subsequent therapies for NSCLC

9.5 Three-monthly Follow-up

The following procedures will be performed approximately every 8 ± 1 weeks for scans and every 3 months ± 7 days (unless otherwise specified) following the End-of-Treatment Visit until death or sponsor decision, whichever comes first:

- Tumor scans until progression for patients who discontinue treatment prior to progression
- Survival status - This may be performed during routine medical visits or by telephone contact.
- Subsequent therapies for NSCLC will be documented during routine medical visits or by telephone contact.

9.6 Methods of Data Collection

9.6.1 Safety Evaluations

9.6.1.1 Adverse Event Assessment

The investigator has the responsibility for assessing the safety of the patients and for compliance with the protocol to ensure study integrity. Patients will be monitored for AEs from the time the first dose of CO-1686 or erlotinib is administered through 28 days after the last dose of protocol-specified treatment. Study procedure-related AEs that occur after signing of the ICF and before administration of CO-1686 or erlotinib will also be collected. Any ongoing SAEs will be followed until resolution or stabilization. AEs and laboratory abnormalities will be graded according to the NCI CTCAE grading system (Version 4.03) and recorded on the eCRF.

Complete details for monitoring AEs, including the definition of drug-related AEs, are provided in Section 10.

9.6.1.2 Clinical Laboratory Investigations

Blood will be analyzed by a local laboratory to inform patient treatment decisions and must be reviewed by the investigator prior to start of CO-1686 or erlotinib administration. Additional tests may be performed at the investigators discretion. The panels of laboratory tests to be performed are shown below.

Hematology: Hemoglobin, hematocrit, WBC and differential (with ANC), reticulocyte count, and platelet count per the schedule of evaluation at screening, during treatment, and at the

End-of-Treatment Visit. Hematology results must be reviewed by the investigator prior to the start of treatment with CO-1686 or erlotinib.

Patients known to require concomitant therapy with anticoagulant therapy such as warfarin (Coumadin®) should have international normalized ratio (INR) monitored at screening and during the study.

Fasting glucose- for all patients taking CO-1686: must be measured following an 8 hour fast (no food or liquid other than water) at screening, C1D1, C1D4, C1D8, C1D15, C2D1, C2D15, and every Cycle *N* D1 thereafter and at End-of-Treatment Visit, also if clinically indicated on study. Fasting glucose is measured as part of clinical chemistry panel (see below) on all cycles Day 1 visits, and measured individually C1D4, C1D8, C1D15, and C2D15.

In the Phase 2 part only: For crossover patients, fasting glucose will be measured at XO-screening, XO-C1D1, XO-C1D4, XO-C1D8, XO-C1D15, XO-C2D1, XO-C2D15 and every Cycle XO-*N* D1 thereafter and at End-of-Treatment Visit, also if clinically indicated on study. Fasting glucose is measured as part of clinical chemistry panel (see below) on all XO-cycles Day 1 visits, and measured individually on XO-C1D4, XO-C1D8, XO-C1D15, and XO-C2D15.

Clinical chemistry: Total protein, albumin, creatinine, BUN or urea, total bilirubin, alkaline phosphatase, ALT, AST, total cholesterol, HbA1c, ***fasting*** glucose, sodium, potassium, chloride, CO_2 (or bicarbonate), calcium, magnesium, and phosphorus per the schedule of evaluations at screening, during treatment, and at the End-of-Treatment Visit. Serum levels of AAG will be determined on PK sampling days. HbA1c will be measured at screening and every other cycle (Cycle 3, 5, 7, etc.) while the patient is on study.

Urinalysis: Performed on freshly voided clean sample by dipstick for protein, glucose, blood, pH, and ketones per the schedule of evaluations. If dipstick findings are abnormal, then a microscopic evaluation will be performed to assess the abnormal findings. Urinalysis will be performed at screening only but both in the initial Phase 2 part of the study and at screening for patients who crossover (Phase 2 part only).

Serum ß-hCG pregnancy test: Performed on women of childbearing potential ≤ 3 days before C1D1 and at the End-of-Treatment Visit. If the serum pregnancy test results are not available on C1D1, a urine pregnancy test can be performed at C1D1 to confirm that the patient is not pregnant prior to dosing. Both values should be entered on the eCRF. A negative result must be confirmed by a physician before the first dose of CO-1686 or erlotinib can be administered.

Laboratory reports will be reviewed by the investigator or delegated physician who will then comment on out-of-range parameters and assess clinical significance. Clinically significant abnormalities and associated panel results, as well as results of any additional tests performed as follow-up to the abnormalities, will be documented on the eCRF as an AE.

For patients who report ILD including pneumonitis while on study treatment, diagnostic radiographic imaging should be provided to the sponsor. Such imaging data may be used by the sponsor to perform independent radiographic assessment of the findings.

9.6.1.3 Vital Signs

Vital signs will include blood pressure, pulse, and body temperature. All vital signs will be obtained after the patient has been resting for at least 5 min. Vital signs will be performed at screening and at each study visit, including the End-of-Treatment Visit.

9.6.1.4 12-lead Electrocardiograms

Triplicate serial 12-lead ECGs (10-sec ECG tracings collected in triplicate [as 10 second tracings > 2 min apart]) will be taken anytime at screening, 5 to10 minutes prior to dosing on Day 1 (C1D1, C1D8, C1D15, XO-C1D1, XO-C1D15), and at each cycle study visit, at the End-of-Treatment Visit, and as clinically indicated.

ECGs should be performed after the patient has been resting for at least 5 minutes. The ECGs will subsequently be reviewed by the investigator or delegated physician for treatment decisions. The 12-lead ECGs collected will be analyzed at a central ECG laboratory. Details on recording ECGs and preparation for central interpretation will be included in the investigator's file.

9.6.1.5 Body Weight and Height

Height will be measured only during the screening visit of the main part of the study. Weight will be measured at all study visits (the patient should be in light indoor clothes).

9.6.1.6 Physical Examinations

Physical examinations will include an assessment of all the major body systems.

9.6.1.7 ECOG Performance Status

ECOG performance status (Appendix B) will be assessed at screening, at each study visit, and at the End-of-Treatment Visit. ECOG performance status should be assessed by the same study personnel at each visit, if possible. Care will be taken to accurately score performance status, especially during screening for study eligibility purposes. Additional consideration should be given to borderline ECOG performance status to avoid enrolling patients with significant impairment.

9.6.2 Efficacy Evaluations

9.6.2.1 Tumor Assessments

Tumor assessments will be performed at screening, and every 8 ± 1 weeks thereafter (Day 1 of Cycles 3, 5, 7, etc.) until tumor progression, during the baseline period for patients who crossover (Phase 2 part only) to CO-1686 treatment following progression on erlotinib (scans obtained at progression may be used), and at the End-of-Treatment Visit. For patients with clinical progression, radiographic assessment should be performed to document evidence of radiographic progression. Tumor scans do not need to be repeated at end-of-treatment if < 2 weeks since last scan or the patient had disease progression at the last scan. An MRI may be used in place of a CT at end-of-treatment scan if required per local authorities. Scans will be evaluated locally for patient treatment decisions. Scans will also be collected and stored with a

central vendor and quality control performed; central reading of scans will not be done unless requested by the sponsor. Tumor response will be interpreted using RECIST Version 1.1 (Appendix A).[14]

Patients who continue treatment with CO-1686 or erlotinib post-progression should continue to be scanned according to the protocol until they discontinue from the study.

Patients who discontinue treatment without progression should continue to be scanned every 8 ± 1 weeks per protocol until disease progression occurs.

Tumor assessments should consist of clinical examination and appropriate imaging techniques (preferably CT scans of the chest and abdomen with appropriate slice thickness per RECIST Version 1.1); scans of the pelvis (CT or MRI) are required if there is prior evidence of local disease or if clinically indicated (symptomatic patients); other studies (MRI and X-ray) may be performed if required. The same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study.

Brain imaging (CT/MRI) is required at baseline. Patients with brain lesions detected at baseline will not be eligible for the study. Brain imaging is not required on study unless clinically indicated.

9.6.3 Pharmacokinetic Evaluations and AAG Analysis

For all patients randomized to CO-1686, blood samples will be drawn for CO-1686 POPPK analysis for the first 6 months (Day 1 of Cycles 2 to 7 inclusive for patients randomized to CO-1686 or Day 1 of XO-cycles 2 to 7 inclusive for patients in the Phase 2 part that crossover to CO-1686) after treatment with CO-1686 is initiated. The blood draw will be prior to that days' dosing and the blood draw time relative to the last dosing time will be recorded at each PK sample occasion for each patient.

Serum samples for AAG analysis will be collected on the same day as PK samples.

Central laboratories will be used for bioanalysis of plasma CO-1686 and AAG measurement. Please refer to the laboratory manual for details on collection and processing of blood PK samples.

9.6.4 Biomarker Assessments

EGFR mutational status will be assessed in matching blood and tumor tissue collected at screening from each patient.

For all patients up to 25 mL of whole blood will be collected at screening, at Day 1 of each cycle, Day 15 of Cycle 1, and at the End-of-Treatment Visit and during the baseline period for patients randomized to erlotinib and progressing with confirmed T790M disease at relapse who crossover to CO-1686 treatment (Phase 2 part only), and at the End-of-Treatment Visit. Matched blood sampling should be collected prior to the biopsy procedure, if possible. Blood samples will be processed locally for plasma and stored frozen for subsequent batch shipping to the sponsor's laboratory.

Tumor tissue from the primary tumor, or an accessible metastatic lesion, will be obtained within 60 days prior to dosing. The corresponding blood specimen will be obtained prior to tumor specimen collection where possible. In the Phase 2 part only, in order to be eligible for the crossover portion of the study, erlotinib-treated patients must have an additional biopsy upon progression and within 35 days prior to dosing with CO-1686 to confirm T790M+ status and meet specific eligibility requirements. Following disease progression on randomized treatment, patients who provide additional consent will undergo tumor biopsy before subsequent-line therapy is initiated. To ensure adequate viable tumor tissue is obtained for mutational testing and diagnostic kit development, image-guided biopsies should be achieved with 18- to 20-gauge cutting needles to provide 1 to 3 cores measuring 1 to 1.5 cm in length. Tumor samples will be processed locally to yield formalin-fixed paraffin-embedded (FFPE) tissue blocks.

Blood and tissues specimens collected from patients will be used to investigate the genetic and transcriptional changes associated with response and resistance to erlotinib and CO-1686, for example targeted exon sequencing of 'clinically significant' cancer genes using next-generation sequencing technology. Extracted genomic deoxyribonucleic acid (DNA) from blood may be compared to tumor DNA so that genetic alterations unique to the tumor that may modulate response or resistance to EGFR-targeted therapy can be unambiguously identified.

Biomarker analysis may be performed on a subset of patients if it becomes clear that the analysis will have limited scientific value in some patients (e.g., because of a very low titer of ctDNA), or if there are not enough serially collected samples from individual patients to allow for adequate biomarker evaluation.

For patients who provide additional consent and are randomized to CO-1686, genomic DNA will be extracted from a blood sample in order to detect genetic polymorphisms in CYP isozymes and to explore the possible correlation between CYP polymorphism and CO-1686 drug exposure.

Sample handling instructions will be provided in a separate laboratory manual.

9.6.5 Quality of Life Assessments

QOL will be assessed by measuring PRO using the EORTC QLQ-C30[15] and LC13, the DLQI,[16] and the EQ-5D,[17] which will be administered at screening, predose on C1D1, then every 8 ± 1 weeks for 6 months (Day 1 of Cycles 3, 5, 7, inclusive). After the Cycle 7 Day 1 visit, questionnaires will be collected every 12 ± 1 weeks (Day 1 of Cycles 10, 13, 16, etc) and at end-of-treatment.

In the Phase 2 part only, for patients randomized to erlotinib who are T790M+ at the time of disease progression and switch to CO-1686 in the study, PRO will be measured using the EORTC QLQ-C30 and LC13, the DLQI, and the EQ-5D, which will be administered prior to dosing with CO-1686 and then at the same frequency described in Section 9.3.

9.6.6 Patient Diary

Patient diaries will be provided to patients. Patients will use the diary to note the date, time and dose of CO-1686 or erlotinib administration.

10 ADVERSE EVENT MANAGEMENT

10.1 Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a patient administered a medicinal product that does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational medicinal product. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction, or the significant worsening of the indication under investigation that is not recorded elsewhere on the eCRF under specific efficacy assessments. Anticipated fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening are not considered AEs.

It is the responsibility of the investigator to document all AEs that occur during the study. AEs should be elicited by asking the patient a nonleading question (e.g., “Have you experienced any new or changed symptoms since we last asked/since your last visit?”). AEs will be reported on the AE eCRF. Symptoms reported spontaneously by the patient during the physical examination will also be documented on the AE eCRF (not on the physical examination eCRF, which is reserved for physical signs or findings).

10.2 Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that occurs at any dose of CO-1686 or erlotinib that:

- Results in death. Death may occur as a result of the underlying disease process. Nevertheless, any event resulting in death during the reporting period must be treated as an SAE and reported as such. All deaths occurring within 28 days of the last administration of study treatment should be reported as SAEs.
- Is life-threatening (patient is at immediate risk of death from the event as it occurred)
- Requires in-patient hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect

Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or seizures that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

10.3 Definition of an Adverse Event of Special Interest (AESI)

An AE of special interest (serious or nonserious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., health authorities or ethics committees) might also be warranted.

Details on the sponsor's currently agreed list of AESIs for rociletinib can be found in the current rociletinib Investigator's Brochure. These AESIs are to be reported to the sponsor expeditiously (see Section 10.9 for reporting instructions).

10.4 Events or Outcomes Not Qualifying as Serious Adverse Events

The following are not considered SAEs:

- Pre-planned or elective hospitalization including social and/or convenience situations (e.g., respite care)
- Overdose of either study drug or concomitant medication unless the event meets SAE criteria (e.g., hospitalization). However, the event should still be captured as a non-serious AE on the appropriate eCRF page
- Events of progression of the patient's underlying cancer as well as events clearly related to progression of the patient's cancer (signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal during the study or within the safety reporting period. If the event has a fatal outcome during the study or within the safety reporting period, then the event of Progression of Disease must be recorded as an AE and as an SAE with CTCAE Grade 5 (fatal outcome) indicated.
- Diagnosis of progression of disease or hospitalization due to signs and symptoms of disease progression alone should not be reported as SAEs

10.5 Clinical Laboratory Assessments as Adverse Events and Serious Adverse Events

It is the responsibility of the investigator to assess the clinical significance of all abnormal values as defined by the list of reference ranges from the local laboratory. In some cases, significant changes in laboratory values within the normal range will require similar judgment.

An abnormal laboratory value that is not already associated with an AE is to be recorded as an AE only if any one of the following criteria is met:

- An action on the study drug is made as a result of the abnormality
- Intervention for management of the abnormality is required
- At the discretion of the investigator should the abnormality be deemed clinically significant

10.6 Pregnancy or Drug Exposure During Pregnancy

If a patient becomes pregnant during the study the investigator is to stop dosing with study drug(s) immediately.

A pregnancy is not considered to be an AE or SAE; however, it must be reported to the sponsor using the Pregnancy Report Form within the same timelines as an SAE (Section 10.9). **This applies to female patients as well as female partners of male patients.**

A pregnancy should be followed through to outcome, whenever possible. Once the outcome of the pregnancy is known, the Pregnancy Outcome Report Form should be completed and reported to the sponsor.

AEs or SAEs that occur during pregnancy will be assessed and processed according to the AE or SAE processes using the appropriate AE or SAE forms.

10.7 Recording of Adverse Events, Serious Adverse Events and Adverse Events of Special Interest

Any AE from the time the first dose of CO-1686 or erlotinib is administered through 28 days after the last dose, will be recorded on the AE eCRF. In addition, study procedure-related AEs that occur after signing of the ICF and before first dose of CO-1686 or erlotinib will also be captured on the AE eCRF. Any other AE that occurs prior to first dose of study drug should be recorded on the Medical History eCRF. In order to avoid vague, ambiguous, or colloquial expressions, the AE should be recorded in standard medical terminology rather than the patient's own words. Whenever possible, the investigator should combine signs and symptoms that constitute a single disease entity or syndrome. For example, fever, headache, and nasal discharge may be reported as coryza, if that is a reasonable diagnosis.

The existence of an AE may be concluded from a spontaneous report of the patient; from the physical examination; or from special tests such as the ECG, laboratory assessments, or other study-specified procedure (source of AE).

Each AE is to be evaluated for duration, severity, seriousness, and causal relationship to the investigational drug. The action taken and the outcome must also be recorded.

SAEs that occur during the study or within 28 days after receiving the last dose of protocol-specified treatment, and all AESIs, whether or not related to study drug, must be immediately reported to the sponsor/safety designee within 24 hours of knowledge of the event (Section 10.9). After the 28-day window, only SAEs that are considered treatment-related should be reported. This should be done by faxing or emailing the completed SAE/AESI report to the Sponsor/designee contact provided on the SAE/AESI report form. Information on the follow-up of AEs, SAEs and AESIs is provided in Section 10.8.

10.7.1 Intensity of Adverse Events

The severity of the AE will be graded according to the NCI CTCAE Version 4.03 grading scale.[20] For AEs not covered by NCI CTCAE, the severity will be characterized as mild, moderate, severe, or life-threatening according to the following definitions:

- Mild events are usually transient and do not interfere with the patient's daily activities
- Moderate events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities
- Severe events interrupt the patient's usual daily activities and hospitalization (or prolongation of hospitalization) may be required
- Life-threatening events require urgent intervention to prevent death

10.7.2 Causal Relationship of Adverse Events to Investigational Medicinal Products

Medical judgment should be used to determine the cause of the AE considering all relevant factors such as, but not limited to, the underlying study indication, coexisting disease, concomitant medication, relevant history, pattern of the AE, temporal relationship to the study medication, dechallenge, or rechallenge.

Not Related

- An AE that is clearly due to extraneous causes (e.g., concurrent disease, concomitant medications, disease under study, etc.)
- It does not follow a reasonable temporal sequence from administration of study drug
- It does not follow a known pattern of response to study drug
- It does not reappear or worsen when study drug is restarted
- An alternative explanation is likely but not clearly identifiable

Related

- An AE that is difficult to assign to alternative causes
- It follows a strong or reasonable temporal sequence from administration of study drug
- It could not be reasonably explained by the patient's clinical state, concurrent disease, or other concomitant therapy administered to the patient
- It follows a known response pattern to study drug
- It is confirmed with a positive rechallenge or supporting laboratory data

10.7.3 Outcome and Action Taken

The investigator will record the action taken and outcome for each AE according to the following criteria:

Action Taken with Study Drug

- None
- CO-1686 or erlotinib dose reduced/delayed

- CO-1686 or erlotinib temporarily interrupted
- CO-1686 or erlotinib permanently discontinued
- Other (specify)

Outcome

- Recovered
- Recovered with sequelae
- Improved
- Ongoing
- Death
- Lost to follow-up

10.8 Follow-up of Adverse Events, Serious Adverse Events and Adverse Events of Special Interest

All AEs occurring during the study are to be followed up in accordance with good medical practice until resolved; judged no longer clinically significant; or, if a chronic condition, until fully characterized through 28 days after the last dose protocol-specified treatment. Any SAE/AESI must be followed until resolution or stabilization, or until patient is lost to follow-up.

10.9 Regulatory Aspects of Serious Adverse Event Reporting

All SAEs, AESIs and pregnancy, regardless of relationship to study drug, must be reported to the sponsor/safety designee within 24 hours of knowledge of the event, according to the procedures below. It is important that the investigator provide an assessment of relationship of the SAE to study treatment at the time of the initial report. The Clinical Trial Serious Adverse Event/ Adverse Event of Special Interest (SAE/AESI) Report Form must be used for reporting SAEs.

While not considered an SAE, pregnancy occurring in a female patient or in the female partner of a male patient must also be reported to the sponsor/safety designee as soon as the event is known by the clinical site. If the pregnancy occurs in a female patient, study drug should be stopped immediately. Notification to the sponsor/safety designee should take place via facsimile or email utilizing the Pregnancy Report Form.

Further details on SAE/pregnancy reporting can be found in the Investigator's Site File.

The sponsor or its designee is responsible for submitting reports of AEs associated with the use of the drug that are both serious and unexpected to the US Food and Drug Administration (FDA), according to 21 Code of Federal Regulations (CFR) 312.32 ; to the Japanese Pharmaceuticals and Medical Devices Agency (PMDA); to the European regulatory authorities according to the European Commission Clinical Trials Directive (2001/20/EC); and to other regulatory authorities, according to national law and/or local regulations. All investigators participating in ongoing clinical studies with the study medication will receive copies of these reports for prompt submission to their IRB or IEC. In accordance with the European Commission Clinical Trials Directive (2001/20/EC), the sponsor or its designee will notify the

relevant ethics committees in concerned member states of applicable suspected unexpected serious adverse reactions (SUSARs) as individual notifications or through periodic line listings.

The sponsor or its designee will submit all safety updates and periodic reports to the regulatory authorities as required by applicable regulatory requirements.

11 STATISTICAL METHODS

11.1 Analysis Populations

The following analysis populations are defined for the study:

Intent-to-treat (ITT) population—all randomized patients; the primary efficacy analysis of the Phase 3 part will be performed using the ITT population.

Tumor evaluable population—all patients who received at least 1 dose of first-line CO-1686 or erlotinib, have measureable tumor lesions at baseline, and have at least 1 post-baseline tumor assessment.

Safety population—all patients who have received at least 1 dose of CO-1686 or erlotinib.

11.2 Statistical Methods

11.2.1 General Considerations

Quantitative variables will be summarized using descriptive statistics (N, mean, standard deviation, median, minimum, and maximum) and/or frequency and percentages for medically relevant categories. Categorical variables will be presented using frequencies and percentages.

Kaplan-Meier methodology will be used to summarize time-to-event variables. The number of patients with events and the number of censored patients will also be presented. The stratified logrank test will be used to compare the time-to-event distributions between the randomized treatment groups. The same variables used to stratify the randomization will be used in the stratified analyses. In addition, the Cox proportional hazards model will be used to estimate the HR between the randomized treatment groups.

The Fisher's Exact Test will be used to compare frequencies between treatment groups and the t-test will be used for comparing means between treatment groups.

All data will be used to their maximum possible extent but without any imputations for missing data. Results from Phase 2 and Phase 3 will be presented separately and pooled.

All statistical analyses will be conducted with the statistical analysis software (SAS®) system, Version 9.1 or higher.

11.2.2 Patient Disposition

The frequency and percentage of patients in each analysis population will be presented. The primary reason for discontinuation of CO-1686 or erlotinib will be summarized.

11.2.3 Baseline Characteristics

Baseline characteristics and demographic data will be summarized for the ITT population.

11.2.4 Efficacy Analyses

The efficacy endpoints will be evaluated using RECIST Version 1.1.

11.2.4.1 Primary Endpoint

The primary endpoint of the study is invPFS.

invPFS will be calculated as 1+ the number of days from the date of randomization to disease progression, as determined by the investigator or death due to any cause, whichever occurs first. Patients without a documented event of progression will be censored on the date of their last adequate tumor assessment (i.e., radiologic assessment) or date of randomization if no tumor assessments have been performed.

Kaplan-Meier methodology will be used to summarize invPFS. The stratified logrank and the HR will be used for comparing the invPFS distributions among the CO-1686 and erlotinib-treated patients. The invPFS analysis will be stratified by EGFR mutation status (L858R, exon 19 deletion, or other) and territory of residence at time of randomization (Asia vs non-Asia). If the exon 19 deletion subgroup or other mutation subgroup has fewer than 30 patients than these subgroups will be combined for this analysis.

A PFS sensitivity analysis based on an independent radiographic review (irrPFS) will be performed. The irrPFS is defined as the time from randomization to disease progression according to RECIST v1.1 as assessed by independent radiographic review, or death due to any cause, whichever occurs first.

11.2.4.2 Secondary Efficacy Endpoints

OBJECTIVE RESPONSE RATE

The ORR is the proportion of patients with a best overall response of partial response (PR) or CR recorded from the start of the treatment until disease progression or recurrence. The frequency and percentages of patients with a best overall response of CR, PR, stable disease (SD), or progressive disease (PD) will also be summarized.

The frequency of patients with CR or PR will be compared between treatment groups using the Fisher's Exact Test.

DURATION OF RESPONSE

The DR for CR and PR will be measured from the date that any of these best responses is first recorded until the first date that PD is objectively documented. DR will be summarized using descriptive statistics (N, mean, standard deviation, median, minimum, and maximum) as well as categorically. For patients who continue treatment post-progression, the first date of progression will be used for the analysis.

PATIENT REPORTED OUTCOMES (QUALITY OF LIFE)

QOL will be measured using the PROs of EORTC QLQ-C30, EORTC QLQ-LC13, the DLQI, and the EQ-5D.[15-17]

The EORTC questionnaires will be scored using the published scoring algorithms provided by the EORTC. For each item or scale, a linear transformation will be applied to standardize the raw score to a range from 0 to 100. A high scale score represents a higher response level.

Thus a **high score for a functional scale** represents a *high / healthy level of functioning*, a **high score for the global health status / QOL** represents a *high QOL*, but a **high score for a symptom scale / item** represents a *high level of symptomatology / problems*.

The baseline PRO measurement will be defined as the last value prior to or on the day of the first dose of CO-1686 or erlotinib. The on-treatment period will be defined as the day after the first dose of CO-1686 or erlotinib to 28 days after the last dose of protocol-specified treatment. QOL measurements collected during the on-treatment period will be included in the summary tables.

The summary of PRO data will include descriptive statistics (N, mean, standard deviation, minimum, median, and maximum) of the observed measurements at each visit during the on-treatment period. Summaries using descriptive statistics of the change or percent change from baseline to each visit during the on-treatment period may also be provided. Graphical presentations may be used to present the mean changes over time.

The time to a worsening in symptoms will be computed as 1+ the number of days from the date of randomization to the first instance of a $\geq$ 10 point increase from baseline in symptoms. Patients without an event will be censored on the date of their last assessment. Kaplan-Meier methodology will be used to summarize the time deterioration and the treatment groups will be compared using the logrank test and hazard ratio.

Analyses of changes and/or percent changes from baseline will be analyzed for each scheduled post-baseline visit and for the final visit for the EQ-5D instrument and the EQ-VAS. If more than one measurement exists for a patient on a particular day, then an arithmetic average will be calculated. This average will be considered to be that patient's measurement for that day. Post-baseline measurements more than 28 days after the last dose of protocol-specified treatment will not be included. Patients that do not have both a baseline measurement and at least one post-baseline measurement will not be included.

At a given visit, the change and/or percent change from baseline will be compared between the randomized treatment groups using an analysis of covariance (ANCOVA), using the treatment as a categorical factor and baseline measurement for the parameter as a continuous covariate.

OVERALL SURVIVAL

OS will be calculated as 1+ the number of days from the first dose of study drug to death due to any cause. Patients without a documented date of death will be censored on the date the patient was last known to be alive.

Kaplan-Meier methodology will be used to summarize OS and the treatment groups will be compared using the logrank test.

POPULATION PK ANALYSES

Sparse blood sampling for POPPK analyses will be conducted in all patients initially randomized and treated with CO-1686. A specific population PK data analysis plan will be developed and will outline the detailed approach to data handling, model development and diagnostics, individual model parameter estimation, exploration of covariate effects, and final model evaluation techniques.

11.2.5 Safety Analyses

The safety analyses will be performed using the safety population (all patients who have received at least 1 dose of CO-1686 or erlotinib).

11.2.5.1 Extent of Exposure

The following will be summarized by dose group:

- Number of cycles initiated
- Number of dose reductions, delays or interruptions
- Duration of exposure

The number of cycles initiated will be investigated by summarizing the number of cycles started by each patient. The number of patients with at least one dose reduction, delay or interruption will be summarized with frequencies and percentages.

11.2.5.2 Adverse Events

The severity of the toxicities will be graded according to the NCI CTCAE Version 4.03 whenever possible. Treatment-emergent AEs are defined as AEs with an onset date on or after the date of first dose of CO-1686 or erlotinib until the date of the last dose of protocol-specified treatment plus 28 days. AEs will be considered treatment-emergent if all or part of the date of onset of the AE is missing and it cannot be determined if the AE meets the definition for treatment-emergent.

The number and percentage of patients who experienced treatment-emergent AEs for each system organ class and preferred term will be presented by dose group. Multiple instances of the treatment-emergent AEs in each system organ class and multiple occurrences of the same preferred term will be counted only once per patient. The number and percentage of patients with at least one treatment-emergent AE will also be summarized by dose group.

Separate tables will present the following by cohort:

- All treatment-emergent AEs
- Treatment-emergent AEs by CTCAE grade
- Grade 3 or greater treatment-emergent AEs

- Treatment-related, treatment-emergent AEs
- Serious treatment-emergent AEs
- Treatment-emergent AEs with an outcome of death
- Treatment-emergent AEs leading to discontinuation of randomized treatment
- Treatment-emergent AEs resulting in interruption or reduction/delay of randomized treatment

The incidence of treatment-emergent AEs will be summarized by relationship to PO CO-1686 or erlotinib using "treatment-related" and "not treatment-related" categories. If a patient experiences multiple occurrences of the same AE with different relationship categories, the patient will be counted once as a relationship category of treatment-related.

If a patient experiences multiple occurrences of the same AE with different intensity toxicity grades, the patient will be counted once for the maximum (most severe) toxicity grade. AEs with a missing intensity will be presented in the summary table with a toxicity grade of "Missing." For each toxicity grade, the number and percentage of patients with at least 1 treatment-emergent AE of the given grade will be summarized.

Non-treatment-emergent AEs (pretreatment and post-treatment) will be presented in the data listings.

11.2.5.3 Clinical Laboratory Evaluations

Clinical laboratory evaluations include the continuous variables for hematology, serum chemistry, and urinalysis. Laboratory values will be presented in International System of Units. The baseline laboratory value will be defined as the last value prior to or on the day of the first dose of CO-1686 or erlotinib, but prior to receiving study drug. The on-treatment period will be defined as the day after the first dose of CO-1686 or erlotinib to 28 days after the last dose of CO-1686 or erlotinib. Laboratory values collected during the on-treatment period will be included in the summary tables. The laboratory values collected after the on-treatment period will only be presented in the data listings.

The summary of laboratory data will include descriptive statistics (N, mean, standard deviation, minimum, median, and maximum) of the maximum, minimum, and last value during the treatment period by dose group and study phase. Summaries using descriptive statistics of the change from baseline to the maximum, minimum, and last value during the on-treatment period will also be given by dose group and study phase. Separate listings will be produced for clinically significant laboratory abnormalities (i.e., those that meet Grade 3 or 4 criteria according to CTCAE) by dose group.

11.2.5.4 Vital Sign Measurements

The baseline vital sign measurement will be defined as the last value prior to or on the day of the first dose of CO-1686 or erlotinib. The on-treatment period will be defined as the day after the first dose of CO-1686 or erlotinib to 28 days after the last dose of protocol-specified treatment. Vital sign measurements collected during the on-treatment period will be included in the

summary tables. The vital sign measurements collected after the on-treatment period will only be presented in the data listings.

The summary of vital sign data will include descriptive statistics (N, mean, standard deviation, minimum, median, and maximum) of the maximum, minimum, and last value during the on-treatment period by dose group and study phase. Summaries using descriptive statistics of the change from baseline to the maximum, minimum, and last value during the on-treatment period will also be given by dose group.

11.2.5.5 12-lead Electrocardiograms

ECG intervals will be stratified into categories indicative of potential clinical significance. Each patient's maximum QT_CF intervals from the pretreatment visit and treatment period visits will be classified as ≤ 450 ms, > 450 to ≤ 480 ms, > 480 to ≤ 500 ms, and > 500 ms. For each patient's maximum change from the pretreatment ECG visit for QT_C, intervals will be classified into < 30 ms, ≥ 30 to < 60 ms, and ≥ 60 ms. The number and percentage of patients in each classified category will be presented. Additional endpoints will include abnormal T waves and U waves and other ECG intervals and diagnostic parameters.

Descriptive statistics will be used to summarize other ECG parameters of PR, QRS, QT, and RR interval, and the corresponding changes from pretreatment ECG visit at each time point. Plots of the mean QT/QT_C over time for C1D1 and End-of-Treatment/pretreatment ECG day measurements will be provided.

11.2.5.6 Other Safety Measurements

Body weight and ECOG performance status will be summarized with descriptive statistics (N, mean, standard deviation, median, minimum, and maximum). Concomitant medications/procedures will be tabulated and summarized.

11.2.6 Exploratory Analyses

11.2.6.1 Disease Control Rate

The DCR is the percentage of patients with a CR, PR, or SD lasting at least 12 weeks. The frequency and percentages of patients with a best overall response of CR, PR, SD lasting at least 12 weeks, SD lasting less than 12 weeks, or PD will be summarized.

The frequency of patients with CR, PR, SD for > 12 weeks will be compared between treatment groups using the Fisher's Exact Test.

11.2.6.2 Tumor Growth Kinetics

The SLD measurements and/or other measures of tumor burden will be summarized as the percent change from baseline to each scheduled radiographic assessment using descriptive statistics (N, mean, standard deviation, minimum, median, and maximum). The mean percent changes at each scheduled visit will be compared between CO-1686 and erlotinib using the t-test.

In addition, the rate of change from baseline to the nadir and the rate of change from the nadir to disease progression will also be summarized for each treatment group and compared using the t-test.

11.2.6.3 Tissue and Blood Biomarkers

The change from baseline in tissue and blood biomarkers associated with the EGFR signaling pathway will be summarized with descriptive statistics and the t-test will be used to compare the mean changes between CO-1686 and erlotinib at each scheduled visit.

Both the time from randomization to the first observed increase in plasma mutant EGFR levels and the time from first observed increase in plasma mutant EGFR levels to disease progression will be summarized using Kaplan-Meier methodology.

11.2.6.4 Phase 2 Part Only: Subgroup of Patients that Crossover to CO-1686 from Erlotinib

The subgroup of patients that are initially randomized to erlotinib, experience a RECIST radiographic event of disease progression and test positive for the T790M mutation will be allowed to continue in the study after the initial event of disease progression and crossover to treatment with CO-1686.

The efficacy and safety of CO-1686 will be summarized descriptively in this subgroup of patients (treatment-emergent AEs, invPFS, ORR, DR, DCR and OS).

11.3 Sample Size Considerations

Up to 1,200 patients will be randomized in a 1:1 ratio to receive treatment with CO-1686 or erlotinib. In the Phase 2 part, 200 patients will be randomized 1:1 to either CO-1686 500 mg BID or erlotinib 150 mg QD. In the Phase 3 part, up to 1,000 additional patients will be randomized 1:1 to either CO-1686 500 mg BID or erlotinib 150 mg QD into the single (sponsor)-blinded part of this clinical study.

The primary objective of this study is to estimate the relative improvement in PFS for CO-1686 as compared with erlotinib. The median PFS for erlotinib in this patient population is expected to be approximately 10 months. If CO-1686 has a 13 month median PFS then the HR comparing CO-1686 with erlotinib will be approximately 0.80.

For the Phase 3 part of the study, a total of 640 PFS events will provide approximately 80% power to detect a HR of 0.80 at a 0.025 (1-sided) significance level for the comparison of CO-1686 versus erlotinib.

11.4 Interim Analysis

A data monitoring committee (DMC) will periodically review efficacy and safety data to ensure that a positive risk/benefit ratio is maintained throughout the study. For the unblinded Phase 2 part, the DMC will, at a minimum, consist of sponsor designated personnel and the primary investigators, and will review safety approximately every 3 – 6 months. The first DMC meeting will take place once 25 patients have completed 2 cycles on protocol-specified

treatment. For the Phase 3 part, the sponsor will remain blinded to efficacy and safety results aggregated by randomized treatment group and an independent data monitoring committee (IDMC) will review safety data on a quarterly basis for the first year, and meet at least twice a year thereafter.

In addition to the aforementioned safety analyses, the IDMC will be convened for up to 3 formal interim efficacy analyses. These analyses will be triggered by randomization of the 600th, 700th, and 800th patients into the Phase 3 part. The formal interim efficacy analyses are based on a Bayesian adaptive design that combines the data from the Phase 2 and Phase 3 parts. If the combined data indicate a high probability (> 99%) of success for the Phase 3 part of the study, then enrollment into the Phase 3 part of the study may be stopped prior to enrollment of 1,000 patients. The study will end when at least 70% of the randomized patients in the Phase 3 part have experienced a PFS event. If timing of the interim efficacy and safety analyses fall within 2 months of each other, then the sponsor may request to combine such IDMC reviews.

12 PATIENT DISPOSITION

12.1 Patient Discontinuations

A patient must be discontinued from protocol-prescribed therapy if any of the following apply:

- Consent withdrawal at the patient's own request or at the request of their legally authorized representative
- Radiographically documented progression of patient's underlying disease, except as noted in Section 5.1.2. If clinical progression is diagnosed then confirmation with CT scan or by MRI will be required before patient withdrawal
- Any event, adverse or otherwise, that, in the opinion of the investigator, would pose an unacceptable safety risk to the patient
- An intercurrent illness that, in the opinion of the investigator, would affect assessments of the clinical status to a significant degree and requires discontinuation of therapy
- A positive pregnancy test at any time during the study
- Noncompliance as described in Section 7.7
- Investigator decision

In addition, the sponsor may discontinue the trial early for any of the reasons noted in Section 13.6.

The sponsor (or designee) should be notified of all study terminations as soon as possible. The date and reason for cessation of CO-1686 or erlotinib must be documented in the eCRF and source documents.

To the extent possible, end-of-treatment procedures should be performed on all patients who receive CO-1686 or erlotinib. The End-of-Treatment Visit should occur 28 (± 7) days following the last dose of CO-1686 or erlotinib. After stopping protocol-specified treatment, all patients will remain in the study and will be followed for safety (through 28 days after last dose; those with ongoing SAEs will be followed until either resolution or stabilization has been determined), for disease progression (every 8 ± 1 weeks until disease progression), and for survival status and subsequent NSCLC therapies (at approximately 3-monthly intervals until death).

13 STUDY ADMINISTRATION

13.1 Regulatory and Ethical Considerations

This study will be conducted in compliance with the protocol; Good Clinical Practices (GCPs), including International Conference on Harmonization (ICH) Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines; FDA regulatory requirements; and in accordance with the ethical principles of the Declaration of Helsinki.

13.1.1 Regulatory Authority Approvals

The sponsor or designee will submit the study protocol plus all relevant study documents to concerned regulatory agencies for approval prior to the study start. No patient will be admitted to the study until appropriate regulatory approval of the study protocol has been received.

Each investigator must complete a Form FDA 1572 and provide the completed form according to written instructions to the sponsor (or designee). Each investigator must submit to the sponsor (or designee) financial disclosure information according to national law and/or local regulations.

US-generated data will be handled in accordance with the Health Information Portability and Accountability Act (HIPAA). The trial will be registered as required by regulatory authorities including www.clinicaltrials.gov using the Protocol Registration System.

13.1.2 Independent Ethics Committee/Institutional Review Board

This protocol and any material to be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to an IEC/IRB. This also applies to protocol amendments.

The sponsor will supply relevant data for the investigator to submit the study protocol and additional study documents to the IEC/IRB. The principal investigator will submit the study protocol for review and approval by an IEC/IRB, according to national law and/or local regulations, and will provide the IEC/IRB with all appropriate materials.

Verification of the IEC's/IRB's unconditional approval of the study protocol and the written ICF will be transmitted to the sponsor. This approval must refer to the study by exact study protocol title and number, identify the documents reviewed, and state the date of the review.

No patient will be admitted to the study until appropriate IEC/IRB approval of the study protocol has been received, the investigator has obtained the signed and dated ICF, and the sponsor is notified.

The principal investigator will submit appropriate reports on the progress of the study to the IEC/IRB at least annually in accordance with applicable national law and/or local regulations and in agreement with the policy established by the IEC/IRB and sponsor.

The IEC/IRB must be informed by the principal investigator of all subsequent study protocol amendments and of SAEs or SUSARs occurring during the study that are likely to affect the safety of the patients or the conduct of the study.

13.2 Confidentiality of Information

The investigator must assure that patients' anonymity is strictly maintained and that their identities are protected from unauthorized parties. Only patient initials and an identification code (i.e., not names) should be recorded on any form submitted to the sponsor and the IEC/IRB. The investigator must keep logs on screened and enrolled patients. In addition, the investigator must have a list where the identity of all treated patients can be found.

The investigator agrees that all information received from Clovis, including, but not limited to, the Investigator's Brochure, this protocol, eCRFs, the protocol-specified treatment, and any other study information, remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study center to any third party or otherwise into the public domain.

13.3 Patient Informed Consent

All information about the clinical study, including the patient information and the ICF, is prepared and used for the protection of the human rights of the patient according to ICH GCP guidelines and the Declaration of Helsinki.

It is the responsibility of the investigator to obtain signed ICFs from each patient participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and prior to undertaking any study-related procedures.

The ICF, prepared by the investigator with the assistance of the sponsor, must be approved along with the study protocol by the IEC/IRB and be acceptable to the sponsor.

The patient must be provided with the patient information and ICF consistent with the study protocol version used and approved by the relevant IEC/IRB. The ICF must be in a language fully comprehensible to the prospective patient. Patients (and/or relatives, guardians, or legal representatives, if necessary) must be given sufficient time and opportunity to inquire about the details of the study and to discuss and decide on their participation in the study with the investigator concerned. The patient and the person explaining about the study and with whom they discuss the informed consent will sign and date the ICF. A copy of the signed ICF will be retained by the patient and the original will be filed in the investigator file unless otherwise agreed.

13.4 Study Monitoring

A Monitor will contact and visit the investigator at the study center prior to the entry of the first patient and as necessary during the study until after the last patient has completed. A monitor will also perform a study closure visit.

In accordance with ICH GCP guidelines, the investigator must ensure provision of sufficient time, reasonable space, and adequate qualified personnel for the monitoring visits. The visits are for the purpose of verifying adherence to the study protocol and the completeness, consistency, and accuracy of data entered on the eCRF and other documents.

The investigator will make all source data (i.e., the various study records, laboratory test reports, other patient records, drug accountability forms, and other pertinent data) available for the monitor and allow access to them throughout the entire study period. Monitoring is done by comparing the relevant site records of the patients with the entries on the eCRF (i.e., source data verification). It is the monitor's responsibility to verify the adherence to the study protocol and the completeness, consistency, and accuracy of the data recorded on the eCRFs.

Drug accountability will be performed as described in Section 7.5. The Investigator Site File will be reviewed to ensure all regulatory documents (e.g., IRB/IEC approvals, approved ICFs, SAE reporting to IRB/IEC, etc.) are present.

By agreeing to participate in the study, the investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of the monitoring visits are resolved. Contact information for the study monitor is located in the investigator file. Representatives from the sponsor may also contact and visit the investigators and monitor data during the study.

13.5 Case Report Form

The data will be collected using an electronic data capture (EDC) system by remote data entry on eCRFs. Sites will receive training on the EDC system. All users will be supplied with unique login credentials.

Prior to study start, the investigator will prepare a list showing the signature and handwritten initials of all individuals authorized to make or change entries on eCRFs. This "study center personnel and delegation list" must be kept current throughout the study.

For each patient enrolled, an eCRF must be completed and reviewed by the principal investigator or co-investigator within a reasonable time period (< 2 weeks) after data collection. This also applies to records for those patients who fail to complete the study. If a patient withdraws or is withdrawn from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

All laboratory data and investigator observations on the results and any other clinically significant test results must be documented on eCRFs.

Full information regarding EDC and completing eCRFs is included in the investigator files. All questions or comments related to electronic capture should be directed to the appropriate Sponsor contact or assigned monitor.

13.6 Study Termination and Site Closure

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures. In terminating the study, the sponsor and the investigator will assure that adequate consideration is given to the protection of the patients' interests.

The sponsor reserves the right to discontinue the study at any time for medical or administrative reasons. When feasible, a 30-day written notification will be given.

The entire study will be stopped if:

- The protocol-specified treatment is considered too toxic to continue the study
- Evidence has emerged that, in the opinion of the sponsor or the investigator(s), makes the continuation of the study unnecessary or unethical
- The stated objectives of the study are achieved
- The sponsor discontinues the development of CO-1686

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded on the eCRF. All reasons for discontinuation of treatment must be documented. In terminating the study, the investigator will ensure that adequate consideration is given to the protection of the patients' interests.

13.7 Modification of the Study Protocol

Protocol amendments, except when necessary to eliminate an immediate hazard to patients, must be made only with the prior approval of the sponsor. Agreement from the investigator must be obtained for all protocol amendments and amendments to the informed consent document. The IEC/IRB must be informed of all amendments and give approval prior to their implementation. The sponsor will submit any study protocol amendments to the concerned regulatory authorities for approval and keep the investigator(s) updated as detailed in the ICH GCP guidelines.

13.8 Retention of Study Documents

The study site will maintain a study file, which should contain, at minimum, the Investigator's Brochure, the protocol and any amendments, drug accountability records, correspondence with the IEC/IRB and the sponsor, and other study-related documents.

The investigator agrees to keep records and those documents that include (but are not limited to) the identification of all participating patients, medical records, study-specific source documents, source worksheets, all original signed and dated ICFs, copies of all eCRFs, query responses, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities and the sponsor or its designees.

The investigator shall retain records required to be maintained for a period of 5 years following the date a marketing application in an ICH region is approved for the drug for the indication for which it is being investigated or, if no application is to be filed or if the application is not approved for such indication, until at least 5 years after the investigation is discontinued. However, these documents should be retained for a longer period if required by the applicable regulatory requirement(s) or if needed by the sponsor. In addition, the investigator must make provision for the patients' medical records to be kept for the same period of time.

No data should be destroyed without the agreement of the sponsor. Should the investigator wish to assign the study records to another party or move them to another location, the sponsor must be notified in writing of the new responsible person and/or the new location. The sponsor will inform the investigator, in writing, when the trial-related records are no longer needed.

Patients' medical records and other original data will be archived in accordance with the archiving regulations or facilities of the investigational site.

13.9 Clinical Study Report

A clinical study report will be prepared under the responsibility and supervision of the sponsor and signed by the sponsor's chief medical officer, thereby indicating their agreement with the analyses, results, and conclusions of the clinical study report.

13.10 Study Publication

All data generated from this study are the property of the sponsor and shall be held in strict confidence along with all information furnished by the sponsor. Independent analysis and/or publication of these data by the investigator(s) or any member of their staff are not permitted without the prior written consent of the sponsor. Written permission to the investigator will be contingent on the review by the sponsor of the statistical analysis and manuscript, and will provide for nondisclosure of the sponsor confidential or proprietary information. In all cases, the parties agree to submit all manuscripts or abstracts to all other parties 30 days prior to submission. This will enable all parties to protect proprietary information and to provide comments based on information that may not yet be available to other parties.

13.11 Quality Assurance Audits

An audit visit to clinical centers may be conducted by a quality control auditor appointed by the sponsor. The purpose of an audit, which is independent of and separate from routine monitoring or quality control functions, is to evaluate trial conduct and compliance with the protocol, SOPs, ICH GCPs, and the applicable regulatory requirements. The investigator and the sponsor may also be subject to an inspection by FDA, European Regulatory authorities, or other applicable regulatory authorities at any time. The auditor and regulatory authorities will require authority from the investigator to have direct access to the patients' medical records. It is important that the investigator(s) and their staff cooperate with the auditor or regulatory authorities during this audit or inspection.

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15 APPENDICES

Appendix A. Response Evaluation Criteria in Solid Tumors Criteria

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Appendix A

Response Evaluation Criteria in Solid Tumors Criteria

The RECIST guidelines (Version 1.1) are described in Eisenhauer (2009)[14] and at http://www.eortc.be/Recist/Default.htm. A short summary is given below.

Measurable Disease:

Tumor lesions: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) with the following:

1. A minimum size of 10 mm by CT scan (CT scan thickness no greater than 5 mm).

2. A minimum size of 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as non-measurable).

3. A minimum size of 20 mm by chest X-ray.

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be not greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable Disease:

All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions, are considered non-measurable disease. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitic involvement of skin and lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Bone Lesions

Bone lesions, cystic lesion, and lesions previously treated with local therapy require particular comment. Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic–blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are non-measurable.

Cystic Lesions

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) because they are, by definition, simple cysts.

Cystic lesions thought to represent cystic metastases can be considered as measurable lesions if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred as target lesions.

Lesions with Prior Local Treatment

Tumor lesions situated in a previous irradiated area or in an area subjected to other locoregional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

Target Lesions

All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target Lesions

RECIST criteria require unequivocal quantification of the changes in tumor size for adequate interpretation of the sum of target lesions. Consequently, when the boundaries of the primary are difficult to delineate, this tumor should not be considered a target lesion.

Guidelines for Evaluation of Measurable Disease

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Evaluation of Target Lesions

Complete Response	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial Response	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD.
Stable Disease	Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.
Progressive Disease	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.

Evaluation of Non-target Lesions

Complete Response	Disappearance of all non-target lesions and normalization of tumor marker level.
Stable Disease/Incomplete Response	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.
Progressive Disease	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

If tumor markers are initially above the institutional ULN, they must normalize for a patient to be considered a complete *responder.*

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Time Point Response

A response assessment will occur at the protocol-specified time points. The tables below provide a summary of the overall response status calculation at each time point for patients who have measureable and non-measureable disease (non-target disease only).

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 evaluated	No	PR
SD	Non-PD or not evaluated	No	SD
Not Evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

NE = Not evaluable

Evaluation of 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

[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 this 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.

Missing Assessments and Not Evaluable Designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an

assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response, which is most likely to occur in the case of PD; e.g., if only 2 of 3 baseline target lesions are assessed and result in a > 20% increase in the sum, then the patient would be assessed as a PD regardless of the missing lesion.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having symptomatic deterioration. Every effort should be made to document the objective progression, even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (FNA/biopsy) prior to confirming the complete response status.

Confirmatory Measurement/Duration of Response

Confirmation

CT scans are required every 8± 1 weeks. If an initial CR or PR is noted, confirmatory scans must be performed 4 ± 1 week later. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of no less than 4 ± 1 weeks.

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease

SD is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Appendix B

Eastern Cooperative Oncology Group Performance Status Scale

ECOG Performance Status	
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 or 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.

Appendix C

Inhibitors and Inducers of CYP2C8, CYP2D6 and P-gp

The following list of inhibitors and inducers of CYP2C8, CYP2D6 and P-gp are to be avoided or used with caution in patients receiving CO-1686. Selection of an alternative concomitant medication with no or minimal enzyme inhibition or induction potential is recommended.

Inhibitors and Inducers of CYP2C8 and CYP2D6

CYP Enzyme	**Inhibitors (Avoid)**	**Inducers (Caution)**
CYP2C8	gemfibrozil trimethoprim glitazones montelukast quercetin	rifampin
CYP2D6	bupropion fluoxetine paroxetine quinidine	

Inhibitors and Inducers of P-gp

Enzyme	Inhibitor (Caution)	Inducer (Caution)
P-gp	amiodarone azithromycin captopril carvedilol clarithromycin conivaptan cyclosporine diltiazem dronedarone erythromycin felodipine itraconazole ketoconazole lopinavir ritonavir quercetin quinidine ranolazine verapamil	avasimibe carbamazepine phenytoin rifampin St. John's wort tipranavir/ritonavir

Appendix D

Study CO-1686-022 Extension Phase

OBJECTIVE OF THE EXTENSION PHASE

The purpose of the Extension Phase is to allow patients to continue on study but to avoid unnecessary collection of data that will no longer be analyzed or required for regulatory purposes, whilst maintaining an appropriate level of safety monitoring.

An important change of the Extension phase is the removal of the option for patients to crossover to CO-1686 following radiographic progression on erlotinib. The decision to remove the crossover option to CO-1686 was based on the recommendation of the DMC, which oversees the risk/benefit aspects of the study. Patients and their physicians are directed to seek alternative treatments, which can fulfill this need.

In addition, this amendment also introduces the availability of NAT2 testing for patients, an indirect indicator of the likelihood of developing hyperglycaemia and QTc prolongation. The availability and disclosure of this information to the patients's treating physician will not affect the monitoring and associated treatment guidelines for these adverse events.

Additional information on efficacy/safety aspects
The most current clinical and non-clinical updates, in particular those pertaining to efficacy and safety data, are provided in the current Investigator's Brochure, in which integrated summaries of efficacy and safety data are presented.

Additional information relating to hyperglycemia and QTc prolongation
The polymorphic enzyme NAT2 mediates the N-acetylation of M502 to form M544 and also plays a role in the elimination of M460. NAT2 genotype polymorphism was assessed for the group of patients who received CO-1686 at 500 mg BID, 625 mg BID, 750 mg BID, and 1000 mg BID and who gave additional informed consent for genomic testing. The NAT2 genotype polymorphism testing was performed using an assay based on polymerase chain reaction (PCR) followed by mass spectrometry to identify single nucleotide polymorphisms in NAT2. Based on NAT2 genotype results, patients were classified as having "low", "intermediate", and "rapid" acetylator phenotype.[34] Acetylator status is currently available for 635 patients. Additional testing will be completed as additional samples are received.

Adverse event and laboratory data based on NAT2 phenotype are summarized in Appendix D, Table 1 , Appendix D, Table 2 , and Appendix D, Table 3. Analyses are presented by acetylator status for all doses combined, since the combined-dose findings were consistent with the findings within each dose group.

Appendix D, Table 1 demonstrates that Grade 3 events are less common in patients who are classified as "rapid" acetylators. As expected, the relationship is most clear for hyperglycemia and QT-prolongation, while other adverse events of special interest (AESIs) appear to be less closely associated with acetylator status. Appendix D, Table 2 shows that hyperglycemia appears to be less frequent and less severe in rapid acetylators. Appendix D, Table 3 shows that QTcF prolongation on ECG appears to be less frequent and less severe in rapid acetylators.

Appendix D, Table 1.

Grade 3 or Greater Treatment-emergent Adverse Events by Acetylator Status

	Overall (N = 635)		
	Slow (n=300)	**Intermediate (n=259)**	**Rapid (n=76)**
Overall	243 (81%)	194 (75%)	48 (63%)
Hyperglycemia (CT)	131 (44%)	66 (26%)	13 (17%)
QTc prolongation (CT)	44 (15%)	19 (7%)	1 (1%)
Malignant neoplasm progression	39 (13%)	39 (15%)	8 (11%)
Cataracts (CT)	12 (4%)	9 (4%)	7 (9%)
Pneumonitis (CT)	3 (1%)	4 (2%)	0
Diarrhea	13 (4%)	16 (6%)	1 (1%)

Abbreviation: CT=combined terms.

Appendix D, Table 2. Hyperglycemia Lab-shift by Acetylator Status

	Overall (N = 635)		
	Slow (n = 300)	**Intermediate (n = 259)**	**Rapid (n = 76)**
Subjects with any post-baseline glucose values > 250 mg/dL	121 (40%)	65 (25%)	17 (22%)
Subjects with 2 or more post-baseline glucose values > 250 mg/dL	51 (17%)	36 (14%)	7 (9%)
Subjects with any post-baseline glucose values > 500 mg/dL	11 (4%)	7 (3%)	1 (1%)
Subjects with 2 or more post-baseline glucose values > 500 mg/dL	3 (1%)	0 (0.0)	0 (0.0)

Appendix D, Table 3. QTcF Changes on ECG by Acetylator Status

	Overall (N = 635)		
	Slow (n = 300)	**Intermediate (n = 259)**	**Rapid (n = 76)**
QTcF Post-baseline ≥ 450 msec	198 (66%)	131 (51%)	34 (45%)
QTcF Post-baseline ≥ 481 msec	92 (31%)	44 (17%)	7 (9%)
QTcF Post-baseline ≥ 501 msec	59 (20%)	22 (9%)	1 (1%)
Two of more within 3 days ≥ 501 msec	19 (6%)	10 (4%)	0 (0.0)
QTcF Change from Baseline > 30 msec	246 (82%)	171 (66%)	47 (62%)
QTcF Change from Baseline > 60 msec	141 (47%)	57 (22%)	9 (12%)

Abbreviation: ECG=electrocardiogram.

For those patients ongoing on CO-1686 trials, informed consent and testing for NAT2 polymorphism status will be offered and the results will be shared with the treating physician. It will be up to the patient in consultation with the treating physician to decide continued participation in the trial in light of the acetylator status results or whether alternative treatment options should be sought.

Regardless of acetylator status, monitoring should be the same for all patients receiving CO-1686 whilst on treatment.

STUDY DESIGN

Treatment Regimen and Duration of Therapy

The option to crossover to CO-1686 following radiographic progression on erlotinib will no longer be available to patients in this Extension Phase (see Objective of the Extension Phase).

All patients will sign an informed consent which explains the rationale for closing the CO-1686 clinical development program for NSCLC and the option for ongoing patients to continue receiving study treatment, should they decide to do so and/or if in the opinion of their treating physician they continue to receive clinical benefit. However, the

suitability of alternative treatment options should be considered by the treating physician and discussed with the patient prior to taking the decision to continue treatment with CO-1686 CO-1686 will be administered daily on a 28-day cycle. Dosing will be delayed or decreased according to protocol-specified toxicity criteria (Section 7.4). Each dose should continue to be taken with 8 oz. (240 mL) of water and with a meal or within 30 minutes after a meal two times per day. Tablets should be swallowed whole.

Treatment may continue until disease progression or intolerable toxicity. Please note, patients on CO-1686 or erlotinib, may opt to continue to receive treatment with CO-1686 following radiographic progression as outlined in the NCCN guidelines for treatment of NSCLC with EGFR TKIs if patient provides additional consent, the investigator feels it is in the patient's best interest and with sponsor approval. It is important that before deciding to continue treatment with CO-1686 or erlotinib post progression, in either of the the two stated scenarios , additional treatment options are explored and discussed with the patient by the treating physician. In general, eligible patients may include those with asymptomatic systemic progression or locally symptomatic progression, such as brain metastases amenable to local treatment, with concomitant asymptomatic systemic progression or continued systemic disease control. This must be discussed with the sponsor and will be reviewed on a case-by-case basis.

If a patient continues treatment post-progression, all Extension Phase study assessments should continue per protocol and data should be captured in the eCRF. The patient should be discontinued from treatment once it is clear that no further clinical benefit can be achieved.

Both the hyperglycemia and QTc management guidelines (Section 7.4) should be followed during this extension phase and any modifications/deviations from these guidances should be discussed and agreed upon with the sponsor prior to implementation.

Once study treatment has been discontinued and the End of Treatment visit has been completed, study participation will cease. Investigational centers will interpret tumor scans locally for the purpose of making treatment decisions and for final tumor response evaluation. The study will close once all patients have either completed participation, have transferred to a locally approved treatment access program (e.g. a named patient program) in accordance with relevant local regulations or the sponsor decides to close the study.

PATIENT ELIGIBILITY AND WITHDRAWAL CRITERIA

Eligibility and Number of Patients

This amendment applies to patients who remain on either CO-1686 or erlotinib on the CO-1686-022 study. No additional patients will be enrolled.

Withdrawal Criteria

The patient has the right to stop treatment or to withdraw from the study at any time.

Patients will continue to receive treatment until one of the following cessation criteria applies:

- Consent withdrawal at the patient's own request or at the request of their legally authorized representative.
- Progression of patient's underlying disease.
    - Post-progression treatment is permitted, at the discretion of the Investigator and with the approval of the sponsor.
- Intercurrent illness that prevents administration of treatment
- Any event, adverse or otherwise, that, in the opinion of the investigator, would pose an unacceptable safety risk to the patient.
- Major noncompliance that may affect patient safety.
- Pregnancy.
- Investigator decision.

In addition, the sponsor may discontinue the trial early for any of the reasons noted in Section 13.6 of the protocol.

The date and reason for cessation of treatment will be documented. Patients with ongoing SAEs will be followed until either resolution or stabilization has been determined.

STUDY PROCEDURES

Schedule of Assessments

The procedures and assessments to be performed are outlined in the Schedule of Assessments presented in Appendix D Tables 4. Procedures are synchronized with administration day of treatment unless indicated. The revised evaluations should commence immediately after the patient is consented, maintaining previous treatment cycle and day sequence.

Table 4. Schedule of Assessments for All Patients

Procedure	Prior to beginning Amendment 3 Evaluations	Day 1 of each cycle	End-of-Treatment Visit (28 ± 7 days after last dose)
Informed Consent	X		
Physical Examination including vision check		X	X
Vital Signs[a] and Weight		X	X
Concomitant Medications and Procedures		X	X
Contraceptive Counseling[b]			X
Serum Pregnancy Test[c]			X
Local hematology including reticulocytes[d]		X	X
Local fasting Serum Chemistry[e]		X	X
Adverse events, including SAEs/AESIs[f]		X	X
CO-1686 dispensing/ administration		X	
Patient diary[g]		X	X
ECG Assessments using central ECG machine [h]		X	X
Tumor Scans[i]	To be done per institution standard of care or 8 ± 1 weeks during treatment ; scans are not required at the End of Treatment Visit		
Blood for CYP Evaluation (Optional Sampling)[j]		X[j]	

[a] = Vital signs (blood pressure, pulse, and temperature) taken predose on drug administration days.
[b] = Patients are to continue using effective contraception for 12 weeks after last dose of CO-1686 or 2 weeks after the last dose of erlotinib and report any pregnancies during this period.
[c] = Serum ß-hCG to be evaluated by local lab will be performed only on women of childbearing potential.
[d] = Includes hemoglobin, hematocrit, WBC and differential (with ANC), platelet count, and reticulocyte count - on Day 1 at each cycle, and at end-of-treatment. Blood will be analyzed by a local laboratory to inform patient treatment decisions, and must be reviewed by the investigator prior to start of CO-1686 or erlotinib administration. Additional tests may be performed at the investigator's discretion.
[e] = Includes total protein, albumin, creatinine, BUN or urea, total bilirubin, alkaline phosphatase, ALT, AST, fasting glucose, sodium, potassium, chloride, magnesium, CO2, calcium, phosphorus, total cholesterol, HbA1c - on Day 1 at each cycle, and at end-of-treatment. Samples will be analyzed by a local laboratory. Fast is defined as 8 hour fast (no food or liquid other than water). HbA1c will be measured every other visit (Cycles 3, 5, 7, etc.) after initiating study drug.
[f] = Patients will be monitored for AEs/SAEs/AESIs from the time the first dose of CO-1686 or erlotinib is administered through 28 days after the last dose.
[g]= Patient diaries should be collected and reviewed for compliance at each visit. No diary will be dispensed at end of treatment.
[h]=12-lead ECG (in triplicate, 10-sec tracings > 2 min apart) prior to dosing up to and including Cycle 12, at a minimum. For patients who are ongoing at this time and for whom QT has been < 470 ms throughout the study, ECG monitoring may be subsequently taken every 3rd cycle thereafter. ECGs will be performed and interpreted locally for patient care decisions; however, tracings should be submitted to the central lab for independent evaluation.
[i]=Tumor scans will no longer be required to be submitted to a central reviewer; Disease progression to continue to be assessed locally by the Investigator. If a patient discontinues treatment before progression or is continuing treatment post progression (approval from Sponsor is required), then the decision to conduct additional scans and the frequency of those scans to monitor disease progression will be the responsibility of the treating physician.
[j]= Only one sample is needed and may be collected at any visit to enable NAT2 analysis.

Day 1 of Each Cycle

Patients receiving CO-1686 are to **refrain** from taking their dose of oral CO-1686 at home on the day of their clinic visit (Day 1 of the cycle) because the dose will be taken during the clinic visit. The following procedures will be completed:

- Physical examination
  - Including a vision check as part of a standard physical exam
- Weight
- Vital signs (blood pressure, pulse, and temperature)
- 12-lead ECG (in triplicate, 10-sec tracings > 2 min apart) prior to dosing, up to and including Cycle 12, at a minimum. For patients who are ongoing at this time and for whom QT has been < 470 ms throughout the study, ECG monitoring may be subsequently taken every 3rd cycle thereafter. ECGs will be performed and interpreted locally for patient care decisions; however, tracings should be submitted to the central lab for independent evaluation. ECGs can be collected at any time pre-dose on the day of the scheduled collection.
- Fasting serum chemistry (including fasting glucose). HbA1c will be measured every other cycle (Day 1 of Cycle 3, 5, 7 etc).
- Hematology (including reticulocyte count)
- Concomitant medication and procedures
- AE monitoring (until 28 days after last dose of protocol specified treatment; then only ongoing SAEs assessed as related to the study drug, and AESIs regardless of causality are followed until resolution or stabilization)
- Collection and review of patient diary and CO-1686 drug return. CO-1686 tablets will be dispensed to the patient; patient diary will be provided to the patient
- Tumor assessments will be performed per institution standard of care or every 8± 1 weeks after dosing until disease (tumor or clinical) progression. Disease progression to continue to be assessed locally by the Investigator. If a patient discontinues treatment before progression or is continuing treatment post progression (with approval from Sponsor), then the decision to conduct additional scans and the frequency of those scans to monitor disease progression will be the responsibility of the treating physician.

- (Optional) Blood for CYP Evaluation
  - Patient may consent for optional CYP sample collection if not previously collected already, and have the sample collected for NAT2 analysis
  - Sample should only be collected at a single visit

End of Treatment Visit

The following procedures will be performed for all patients 28 days (±7 days) after the last dose of oral CO-1686 or erlotinib:

- Physical examination
  o Including a vision check as part of a standard physical exam
- Weight
- Vital signs (blood pressure, pulse, and temperature)
- Concomitant medications and procedures since last visit
- 12-lead ECG (in triplicate, 10-sec tracings > 2 min apart)
- Fasting serum chemistry (includes fasting glucose) .
- Hematology (including reticulocyte count)
- Serum pregnancy test for women of childbearing potential
- AEs/SAEs/AESIs monitoring (until 28 days after last dose of oral CO-1686 or erlotinib; then only ongoing serious adverse events (SAEs) are followed until resolution or stabilization)
- Collection and review of patient diary
- Contraceptive counseling