TIGER-2: A Phase 2, Open-label, Multicenter, Safety and Efficacy Study of Oral CO-1686 as 2nd Line EGFR-directed TKI in Patients with Mutant EGFR Non-small Cell Lung Cancer (NSCLC)

Protocol Number:	CO-1686-019
Investigational Product:	CO-1686
IND Number:	[redacted]
EUDRA CT Number	[redacted]
Development Phase:	Phase 2
Indication Studied:	Locally advanced or metastatic NSCLC with mutant epidermal growth factor receptor (EGFR)
Sponsor Name and Address:	Clovis Oncology, Inc. [redacted]
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 Harmonization (ICH) Good Clinical Practices (GCP) Guidelines. Essential study documents will be archived in accordance with applicable regulations.
[redacted]	[redacted]
Amendment 5:Date	16 August 2016
Version:	6.0

CONFIDENTIALITY STATEMENT

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Protocol Approval Signature Page

Protocol: CO-1686-019

Title: TIGER-2: A Phase 2, Open-label, Multicenter, Safety and Efficacy Study of Oral CO-1686 as 2nd Line EGFR-directed TKI in Patients with Mutant EGFR Non-small Cell Lung Cancer (NSCLC)

Date: 16 August 2016

Version: 6.0

[redacted]

Protocol Acceptance Form

Protocol: CO-1686-019

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Date: 16 August 2016

Version: 6.0

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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Protocol Number	CO-1686-019
Title	TIGER-2: A Phase 2, Open-label, Multicenter, Safety and Efficacy Study of Oral CO-1686 as 2nd Line EGFR-directed TKI in Patients with Mutant EGFR Non-small Cell Lung Cancer (NSCLC)
Phase	Phase 2
Introduction	In mid-2015, Clovis submitted a New Drug Application for the use of rociletinib in patients with T790M-positive NSCLC. In June 2016, the FDA issued a Complete Response Letter to Clovis stating that more data is required to approve rociletinib 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 (Amendment 5) 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 C. This schedule replaces all schedules of assessments in Section 9 and should be followed for all patients. In addition, Amendment 5 (Appendix C) also introduces the availability of NAT2 testing for patients, an indirect indicator of the likelihood of developing hyperglycemia 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. For patients who wish to continue rociletinib treatment post progression, it is important that a full exploration of alternative treatment options between patients and their treating physicians takes place. 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 malignancy in 10% to 15% of patients of European descent and approximately 30% of patients of East Asian descent.[1] Patients with the most common EGFR activating mutations, exon 21 L858R and deletions in exon 19, typically have good responses to therapy with first-generation EGFR inhibitors 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 to treatment, progression generally occurs after 9-14 months of erlotinib, gefitinib, or afatinib therapy, driven in approximately 60% of cases by a second-site EGFR mutation in exon 20 called T790M (the "gatekeeper" mutation) which mediates resistance to first- and second-generation EGFR inhibitors.[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 disease is fatal, with a median overall survival (OS) of less than 2 years.[10] 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 cell death in tumor cells with the T790M mutation, thus driving objective tumor responses and providing therapeutic benefit in patients who have acquired T790M-mediated resistance to first-generation EGFR inhibitors. In the first-in-human study, CO-1686-008, in patients with advanced EGFR mutation positive NSCLC and previous treatment with an EGFR inhibitor, no maximum tolerated dose (MTD) was observed and 3 doses levels, 500 mg twice daily (BID), 625 mg BID, and 750 mg BID, were selected for further clinical evaluation of safety, tolerability and efficacy in the expansion cohorts. Maturing data from this study suggest that patients treated with rociletinib at 500 mg BID and 625 mg BID experience responses that are comparable in frequency, depth and duration, with an overall acceptable safety profile for this advanced cancer patient population. To further describe the risk/benefit profile of the CO-1686 500 mg BID dose, additional patients will be enrolled at a starting dose of 500 mg BID in this study (Cohort B). Response Evaluation Criteria In Solid Tumors (RECIST)[11] responses have been observed across the range of doses studied in Phase 1 with CO-1686, and the current objective response rate (ORR) in patients with T790M-positive NSCLC is > 60%. The most common toxicity observed is hyperglycemia, occurring in approximately 30% of patients, which can usually be readily managed with PO 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 goals of protocol CO-1686-019 are to evaluate the antitumor efficacy, safety and population pharmacokinetic (POPPK)/pharmacodynamic relationships of PO single-agent CO-1686, when administered at the therapeutically active doses of 625 mg BID and 500 mg BID to patients with EGFR-mutated, advanced/metastatic NSCLC after failure of 1 previous EGFR-directed TKI. CO-1686 was being developed with a companion diagnostic (Qiagen, United Kingdom) to identify patients whose tumors express activating EGFR mutations as well as the T790M resistance mutation.
Planned Number of Patients	The total enrollment planned for this study is approximately 225 patients. The patients will be enrolled into 2 cohorts: **Cohort A**: Approximately 125 patients with centrally confirmed T790M-positive NSCLC will be enrolled. These patients will be treated at a dose of 625 mg BID.

	Cohort B: Approximately 100 patients will be enrolled in order to include approximately 40 response evaluable, centrally confirmed T790M-negative patients. All Cohort B patients will be treated at a dose of 500 mg BID.
Planned Number of Sites	Approximately 90 investigative sites in the United States (US), Europe, Asia and Australia.
Study Objectives	**Primary Objective** • To evaluate the antitumor efficacy of PO single-agent CO-1686, as measured by ORR, when administered to patients with EGFR-mutated, centrally confirmed T790M-positive and T790M-negative advanced NSCLC after tumor progression on 1 previous EGFR-directed TKI **Secondary Objectives** • To assess clinical efficacy in patients with centrally confirmed T790M-positive NSCLC: disease control rate (DCR), duration of response (DR), PFS, and OS following CO-1686 treatment • To assess quality of life (QoL) by patient-reported outcomes (PRO) following CO-1686 treatment • To evaluate the safety and tolerability of CO-1686 • To determine the pharmacokinetics (PK) of CO-1686 using POPPK methods and explore correlations between PK, exposure, response, and/or safety findings **Exploratory Objectives** • To evaluate clinical benefit of continued CO-1686 treatment following disease progression • To evaluate concordance of mutant EGFR detection between tissue and plasma and assess CO-1686 mediated alterations in mutant EGFR levels over time using circulating tumor deoxyribonucleic acid (ctDNA) obtained from plasma • To explore tissue and blood-based biomarkers that may be predictive of response or primary resistance to CO-1686 and investigate mechanisms of acquired resistance in the tissue and blood of patients who experience clinical progression during treatment with CO-1686
Study Endpoints	**Primary Endpoints** • ORR according to RECIST Version 1.1. For Cohort A, ORR will undergo independent radiology review (IRR) and in Cohort B, scans will be assessed by IRR if needed as a supporting analysis. **Secondary Endpoints** • DR, DCR and PFS according to RECIST Version 1.1 as determined by IRR • ORR, DR, DCR and PFS according to RECIST Version 1.1 as determined by investigator assessment • OS • Change from baseline in PROs using the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30), EORTC Quality of Life Questionnaire Lung Cancer

	module (EORTC QLQ-LC13), and the Dermatology Life Quality Index (DLQI)[12,13] • Treatment-emergent AEs, laboratory abnormalities, and electrocardiogram (ECG) abnormalities • Plasma PK parameters for CO-1686 based on sparse sampling **Exploratory Endpoints** • Time-to-treatment failure • Extra-cranial PFS • Change from baseline in mutant EGFR levels in ctDNA obtained from plasma • Positive and negative percent agreement between blood and tissue results for T790M • Identify biomarkers associated with response or resistance to CO-1686
Study Design	This is a Phase 2, single arm, open-label, dual cohort, multicenter study evaluating the safety and efficacy of CO-1686 administered PO BID to patients with previously-treated mutant EGFR NSCLC. Patients will be enrolled into 2 cohorts. Cohort A will enroll approximately 125 eligible patients who are centrally confirmed T790M-positive and will be treated at 625 mg BID. Cohort B will be a continuation of the study and will enroll up to approximately 100 eligible patients who will be either centrally confirmed T790M-positive or T790M-negative. All patients in Cohort B will be treated at a starting dose of 500 mg BID. The priority for study enrollment will be for all T790M-positive patients to be enrolled into Cohort A first. Once Cohort A is complete, eligible T790M-positive patients will then be enrolled into Cohort B. All eligible T790M-negative patients will be enrolled into Cohort B. All patients (for Cohort A and B) should have experienced disease progression while on treatment with the first single-agent EGFR-directed TKI (EGFR-TKI) for advanced/metastatic NSCLC. One line of chemotherapy prior to the EGFR-TKI treatment is permissible. The study (Cohorts A and B) will consist of a Screening Phase to establish study eligibility and document baseline measurements; an open-label Treatment Phase, in which the patient will receive CO-1686 to ascertain efficacy and safety until disease progression as defined by RECIST Version 1.1, clinical tumor progression, or unacceptable toxicity as assessed by the investigator. For patients with clinical progression, radiographic assessment should be performed to document evidence of radiographic progression. 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,[14] if the patient provides additional consent, the investigator believes it is in the best interest of the patient, and the sponsor approves. 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. Each 28-day period of treatment will represent 1 cycle, with dosing initiated on Cycle 1 Day 1 (C1D1). Dosing will be delayed or reduced according to protocol-specified toxicity criteria. As mentioned above, patients who provide additional consent may continue to receive treatment with CO-1686 post-progression if, in the opinion of the investigator and approved by the sponsor, the patient is still benefitting. Sparse blood sampling for population PK analyses will be conducted in all patients treated with CO-1686. Serial blood sampling for longitudinal quantitative assessment of ctDNA will be conducted. A central laboratory will confirm presence or absence of the T790M mutation in formalin-fixed paraffin-embedded (FFPE) tumor tissue prior to study enrollment. Following disease progression on CO-1686, patients who provide additional consent will undergo tumor biopsy before subsequent-line therapy is initiated. AEs will be collected from the time the first dose of CO-1686 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 will also be captured. All patients will be followed at approximately 2 monthly intervals to determine disease progression (if patient discontinues treatment before progression), survival status and subsequent NSCLC therapy until death or sponsor decision, whichever comes first. After discontinuation of protocol-specified treatment, subsequent anticancer therapy use will be recorded. In mid-2015, Clovis submitted a New Drug Application for the use of rociletinib in patients with T790M-positive NSCLC. In June 2016, the FDA issued a Complete Response Letter to Clovis stating that more data is required to approve rociletinib 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 (Amendment 5) 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 C. This schedule replaces all schedules of assessments in Section 9 and should be followed for all patients. In addition, Amendment 5 (Appendix C) also introduces the availability of NAT2 testing for patients, an indirect indicator of the likelihood of developing hyperglycemia 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.

	For patients who wish to continue rociletinib treatment post progression, it is important that a full exploration of alternative treatment options between patients and their treating physicians takes place. 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.
Study Population	Except where specified, inclusion and exclusion criteria are **applicable to both Cohorts A and B** of the study. <u>Inclusion Criteria</u> All patients must meet all of the following inclusion criteria: 1. Histologically or cytologically confirmed metastatic or unresectable locally advanced NSCLC 2. Documented evidence of a tumor with 1 or more EGFR mutations excluding exon 20 insertion • Disease progression confirmed by radiologic assessment while receiving treatment with the first single agent EGFR-TKI (eg, erlotinib, gefitinib, afatinib, or dacomitinib) o EGFR-TKI treatment discontinued ≤ 30 days prior to planned initiation of CO-1686 (the washout period for an EGFR inhibitor is a minimum of 3 days) o No intervening treatment between cessation of single-agent EGFR-TKI and planned initiation of CO-1686 o Previous treatment with ≤ 1 prior chemotherapy (excluding prior neo-adjuvant or adjuvant chemotherapy or chemoradiotherapy with curative intent) o Any toxicity related to prior EGFR inhibitor treatment must have resolved to Grade 1 or less • Central laboratory confirmation of the presence of the T790M mutation in tumor tissue in Cohort A and the presence or absence of the T790M mutation in tumor tissue in Cohort B. Centrally indeterminate, unknown or invalid specimens are not acceptable. Biopsy material obtained from either primary or metastatic tumor tissue must have been obtained (and sent to the central laboratory) within 60 days prior to dosing study drug but following disease progression on the first EGFR-TKI. 3. Measureable disease according to RECIST Version 1.1 4. Life expectancy of at least 3 months 5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 6. Age ≥ 18 years (in certain territories, the minimum age requirement may be higher, eg age ≥ 20 years in Japan and Taiwan) 7. Adequate hematological and biological function, confirmed by the following laboratory values:

	• Bone Marrow Function
	  o Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
	  o Platelets > 100.0 × 10^9/L
	  o Hemoglobin ≥ 9 g/dL (or 5.6 mmol/L)
	• Hepatic Function
	  o Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 × upper limit of normal (ULN); if liver metastases, ≤ 5 × ULN
	  o Bilirubin ≤ 2 × ULN
	• Renal Function
	  o Serum creatinine ≤ 1.5 × ULN
	• Electrolytes
	  o Potassium and magnesium within normal range. Patients may receive supplements to meet this requirement
	8. Written 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 in the EGFR gene
	2. 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, with no evidence of that cancer currently, are permitted to enroll in the trial provided all chemotherapy was completed > 6 months prior and/or bone marrow transplant > 2 years prior
	3. Known pre-existing interstitial lung disease
	4. **Cohort A only**: Patients with leptomeningeal carcinomatosis are excluded. Other central nervous system (CNS) metastases are only permitted if treated, asymptomatic, and stable (not requiring steroids for at least 4 weeks prior to the start of study treatment). **Cohort B only**: Patients with CNS metastases or leptomeningeal carcinomatosis are excluded.
	5. Treatment with prohibited medications (eg, concurrent anticancer therapy including other chemotherapy, radiation, hormonal treatment [except corticosteroids and megesterol acetate], or immunotherapy) ≤ 14 days prior to treatment with CO-1686
	6. Patients who are currently receiving treatment with any medications that have the potential to prolong the QT interval and the treatment cannot be either discontinued or switched to a different medication before starting CO-1686
	• see http://crediblemeds.org/ for a list of QT-prolonging medications (includes all medication under categories of Known, Possible and Conditional risk of Torsades de Pointes)

	7. Prior treatment with CO-1686, or other drugs that target T790M-positive mutant EGFR with sparing of wild type EGFR eg, AZD9291, HM61713, TAS-121 8. Any of the following cardiac abnormalities or history: • Clinically significant abnormal 12-lead ECG, QT interval corrected using Fridericia's method (QT_CF) > 450 msec • 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 9. Nonstudy-related surgical procedures ≤ 7 days prior to administration of CO-1686. In all cases, the patient must be sufficiently recovered and stable before treatment administration 10. Females who are pregnant or breastfeeding 11. Refusal to use adequate contraception for fertile patients (females and males) while on treatment and for 12 weeks after the last dose of CO-1686 12. Presence of any serious or unstable concomitant systemic disorder incompatible with the clinical study (eg, substance abuse, uncontrolled intercurrent illness including active infection, arterial thrombosis, and symptomatic pulmonary embolism) 13. Any other reason the investigator considers the patient should not participate in the study
Study Treatment	CO-1686 will be administered to patients as PO tablets at a dose of 625 mg BID (Cohort A) or 500 mg BID (Cohort B). Patients will be instructed to take each dose of CO-1686 with a meal or within 30 minutes after a meal.
Dose-Modification Criteria	No dose escalation beyond the starting dose is allowed in either cohort. Dose reduction steps are allowed for each patient, with the overall number of dose reduction steps at the investigator's discretion. Dose reduction should be in increments of 125 mg BID with up to 2 dose reduction steps permitted. Any need for further dose reduction, or dose adjustment to a 3 times daily (TID) regimen should be discussed with the sponsor before implementing. For Grade 3 or 4 hematologic and non-hematologic toxicities (except for nausea/vomiting, alopecia, QT interval corrected for heart rate [QTc] prolongation and hyperglycemia), the dose should be initially reduced by 125 mg BID (to 500 mg BID, if the starting dose was 625 mg BID; or to 375 mg BID, if the starting dose was 500 mg BID). Re-escalation of dose after resolution of AEs must be discussed with, and approved by, the sponsor. ECGs will be measured throughout the study as described in the protocol. If QT_C prolongation of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE v4.03)[15] 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. 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 can be evaluated. 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 Section 7.4 of the protocol.
Concomitant Medications	Supportive care (eg, antiemetics, analgesics for pain control) 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 • Progression of patient's underlying disease, except as described Section 5.1.2 of the protocol • 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 • A positive pregnancy test at any time during the study • Noncompliance as described in Section 7.7 of the protocol • Investigator decision After stopping protocol-specified treatment, all patients will remain in the study and will be followed for safety (through 28 days after last dose), disease progression (if patient discontinues treatment before progression), survival status, and subsequent therapy assessment (approximately every 2 months until death or sponsor decision).
Efficacy Assessments	Efficacy measures will include tumor assessments, preferably by computed tomography (CT) scans of the chest and abdomen with appropriate slice thickness per RECIST Version 1.1; other studies (magnetic resonance imaging [MRI] and X-ray) may be performed if required. Pelvic imaging should be performed if clinically indicated eg, prior or existing site of metastasis or symptomatic. Brain imaging (CT/MRI) is required at baseline. In Cohort A, patients with brain lesions at baseline will require repeat brain imaging as part of the follow-up tumor assessments. In Cohort B, patients with evidence of brain lesions at Screening 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. ± 1 week), including at the End-of-Treatment Visit. Tumor scan at end-of-treatment is not required if patient had radiographic evidence of disease progression on study, or it has been < 2 weeks since last on-study scan. In addition, an MRI may be used in place of a CT at end-of-treatment scan if required per local authorities. For patients with clinical progression, radiographic assessment should be performed to document evidence of radiographic progression. If a patient discontinues treatment before progression, then scans should continue until progression according to the protocol schedule. Exceptions to this requirement may be acceptable based on local institutional or regulatory requests and must be approved in advance by the sponsor. Tumor scans will be assessed by IRR for the primary endpoint evaluation in Cohort A. In Cohort B, scans will be assessed by IRR if needed as a supporting analysis.

Safety Assessments	Safety assessments will include: • AEs • Hematology, including reticulocyte count, clinical chemistry including hemoglobin A1c (HbA1c), and urinalysis • 12-lead ECGs • Physical examination • Vital signs and body weight • Concomitant medications/procedures • ECOG performance status Where applicable, AEs will be classified according to the NCI CTCAE Version 4.03.[15]
Biomarker Assessments	EGFR mutational status will be assessed in matching blood and tumor tissue collected at Screening from each patient. Tumor tissue from the primary tumor, or an accessible local/distal 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. EGFR-mutational status on collected tissue and blood will be assessed by the sponsor. When tissue is available from the baseline tumor biopsy, samples will be tested for other molecular alterations that may modulate response or resistance to EGFR-targeted therapy including but not limited to EGFR gene amplification, MET proto-oncogene (MET) amplification, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (PIK3CA) mutations, and expression of other growth factor receptors and their ligands. Following disease progression on CO-1686, patients who provide additional consent will undergo a tumor biopsy before subsequent line therapy is initiated. This tissue will be analyzed for molecular alterations that modulate resistance to EGFR-targeted therapy. For patients who provide additional consent, genomic deoxyribonucleic acid (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 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. Blood will be collected for detection and quantification of mutant EGFR from plasma. Blood may also be used to test for biomarkers of response or resistance to EGFR-targeted therapy. All patients (Cohorts A and B) will have blood collected during Screening (within 60 days prior to dosing), at Day 1 of each cycle, and at progression. Blood collected at these time points may also be used to test for biomarkers of response or resistance to EGFR-targeted therapy.
Patient Reported Outcome Assessments	PRO will be measured using the EORTC QLQ-C30 and LC13 and the DLQI,[12,13] 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, ± 1 week). After Cycle 7, questionnaires will be collected every 12 ± 1weeks (Day 1 of Cycles 10, 13, 16, etc, ± 1 week) and at end-of-treatment.

Statistical Procedures

Analysis Populations

- Tumor evaluable population–all patients who received at least 1 dose of CO-1686, have at least 1 measureable tumor lesion at baseline and have at least 1 post-baseline tumor assessment as assessed by IRR (Cohort A) or investigator assessment (Cohort B)
- Safety population–all patients who have received at least 1 dose of CO-1686

Sample Size Justification

Cohort A: Approximately 125 patients will be enrolled. The ORR will be presented with 95% confidence intervals (CIs). The following table provides the 95% CIs for observed response rates of 30%, 40%, and 50% assuming a total of 125 patients.

Confidence Intervals for Observed Response Rates	
Number of Patients	**ORR (%) [95% CI]**
125	30 [22, 39]
125	40 [31, 49]
125	50 [41, 59]

Cohort B: Approximately 100 patients will be enrolled with the aim to include approximately 40 response evaluable, centrally confirmed T790M-negative NSCLC patients. To be response evaluable, patients should have received at least one cycle of therapy, and have had their disease re-evaluated by radiological assessment.

An exact binomial test with a nominal 0.10 2-sided significance level will have approximately 90% power to detect the difference between a null hypothesis response rate of 20% and a clinically meaningful response rate of 40% when the sample size is 40.

Efficacy Analysis

The ORR in both centrally confirmed T790M-positive and centrally confirmed T790M-negative patients will be summarized separately with frequencies and percentages. The DR for complete response (CR) and partial response (PR) for both centrally confirmed T790M-positive and centrally confirmed T790M-negative patients will be summarized separately with descriptive statistics (N, mean, standard deviation, median, minimum, and maximum) as well as categorically.

DCR is defined as the percentage of patients who have achieved CR, PR, and stable disease (SD). Kaplan-Meier methodology will be used to summarize PFS and OS.

Safety Analyses

Data from all patients who receive 1 or more doses of CO-1686 will be included in the safety analyses. AEs, clinical laboratory information, vital signs, ECOG performance status and concomitant medications/procedures will be tabulated and summarized.

Population PK

Sparse blood sampling for POPPK analyses will be conducted in all patients treated with CO-1686. A specific POPPK 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.

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AAG	alpha-1 acid glycoprotein
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
$AUC_{0–24}$	area under the curve from time zero to 24 hours
β-hCG	β subunit of hCG gonadotropin
BID	twice daily
BUN	blood urea nitrogen
C1D1	Cycle 1 Day 1
CFR	Code of Federal Regulations
CI	confidence interval
CO-1686 free base	free base form of CO-1686
CO-1686 HBr	hydrobromide salt formulation CO-1686
C_{max}	maximum concentration
CNS	central nervous system
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
DNA	deoxyribonucleic acid
DR	duration of response
EC	European Commission
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

EOT	end-of-treatment
EURTAC	EURopean TArceva® (erlotinib) versus Chemotherapy study
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FG	fasting plasma or serum glucose
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GRAS	generally regarded as safe
HbA1c	hemoglobin A1c
HBr	hydrobromide
HIPAA	Health Information Portability and Accountability Act
HR	hazard ratio
ICH	International Conference on Harmonization
ICF	Informed Consent Form
IEC	Independent Ethics Committee
INR	international normalized ratio
iPASS	Iressa™ Pan-ASia Study
IRB	Institutional Review Board
IRR	Independent Radiology Review
MedDRA	Medical Dictionary for Regulatory Activities
MET	MET proto-oncogene
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	not evaluable
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
OS	overall survival
ORR	objective response rate
PD	progressive disease
PET	positron emission tomography
PFS	Progression-free survival
P-gp	P-glycoprotein
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PO	Orally

POPPK	population pharmacokinetics
PR	partial response
PRO	patient-reported outcomes
PT	preferred term
QD	once daily
QoL	quality of life
QTc	QT interval corrected for heart rate
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
SD	stable disease
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
$T_{1/2}$	elimination half-life
T790M	EGFR mutation in exon 20, gatekeeper mutation
TID	three times daily
TKI	tyrosine kinase inhibitor
T_{max}	time to maximum concentration
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
WBC	white blood cell
WT	wild-type

3 INTRODUCTION

3.1 CO-1686 Clinical Development Program Update

In mid-2015, Clovis submitted a New Drug Application for the use of rociletinib in patients with T790M-positive NSCLC. In June 2016, the FDA issued a Complete Response Letter to Clovis stating that more data is required to approve rociletinib 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.

3.1.1 Extension Phase

The purpose of this protocol amendment (Amendment 5) 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 C. This schedule replaces all schedules of assessments in Section 9 and should be followed for all patients.

In addition, Amendment 5 (Appendix C) also introduces the availability of NAT2 testing for patients, an indirect indicator of the likelihood of developing hyperglycemia 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.

For patients who wish to continue rociletinib treatment post progression, it is imporatant that a full exploration of alternative treatment options between patients and their treating physicians takes place.

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.

3.2 Mutant EGFR Non-small Cell Lung Cancer

Despite years of research and prevention strategies, lung cancer remains the most common cancer worldwide with an incidence of 1.8 million in 2012 representing 13% of all cancers, and non-small cell lung cancer (NSCLC) accounts for almost 89% of all lung cancers.[16,17] Additionally, lung cancer continues to be the most common cause of cancer-related deaths worldwide with a 5 year survival rate of less than 10% in patients with advanced disease.[18]

Cytotoxic chemotherapy has been the mainstay of treatment of patients with 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 that have demonstrated superiority to chemotherapy in those patients whose tumors express the targeted genetic mutation.

One timely example is the recent approval of crizotinib, used to treat NSCLC patients whose tumors harbor anaplastic lymphoma kinase (ALK) rearrangements. In 2 single-arm studies of crizotinib in previously treated ALK-positive patients, the tumor response rates were 50% and 61% and the duration of responses (DR) were 42 and 48 weeks, respectively.[19,20] These response rates and the DR are significantly higher that what would be expected with chemotherapy in this patient population.[21]

Molecularly targeted therapies also have proven to be superior to chemotherapy for NSCLC patients whose tumors have mutations in the epidermal growth factor receptor (EGFR). Activating EGFR mutations are key drivers of NSCLC malignancy in 10% to 15% of patients of European descent and approximately 30% of patients of East Asian descent.[1] Two recent Phase 3 trials comparing EGFR tyrosine kinase inhibitors (TKIs) versus chemotherapy have established TKIs as the gold standard for treating EGFR-mutation-positive NSCLC. In the Iressa™ Pan ASia Study (iPASS), treatment with gefitinib was compared with 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 with 6.3 months for those on chemotherapy.[22] Quality of life (QoL) was also evaluated in this study; more patients treated with gefitinib versus chemotherapy had clinically meaningful improvement in QoL, as assessed by the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire and the Trial Outcome Index (TOI). Although survival was an endpoint of the study, the analysis of overall survival (OS) was complicated by the fact that EGFR-mutation-positive patients assigned to the chemotherapy arm crossed over to gefitinib upon progression. A second Phase 3 randomized trial, the EURopean TArceva® (erlotinib) versus Chemotherapy (EURTAC) study, compared erlotinib treatment with chemotherapy in previously untreated patients with EGFR mutation-positive NSCLC. Patients demonstrated a response rate of 58% in the erlotinib arm compared with 15% in the chemotherapy arm ($p < 0.0001$). Furthermore, PFS was 9.7 months in the erlotinib arm versus 5.2 months in the chemotherapy arm (hazard ratio [HR] = 0.37; $p < 0.0001$).[23] At an interim analysis, OS was 22.9 months in the erlotinib arm and 18.8 months in the chemotherapy arm (HR = 0.80; $p = 0.42$). Again, cross over from chemotherapy to erlotinib confounds interpretation of survival data in this study. These data demonstrate that gefitinib and erlotinib improve response rates and PFS compared with chemotherapy.

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

Despite the initial response, progression occurs in most patients. In the most comprehensive analysis to date, Sequist et al analyzed serial biopsies from EGFR-mutation-positive NSCLC patients who progressed on TKIs.[23] Through this research, Sequist demonstrated that acquired resistance occurs through a number of different mechanisms, while the activating mutation is

maintained. The most common cause of progression (in 60% 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.[3,8,9,23] This mutation 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] 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.[23]

The differences in the mechanisms of resistance have a direct impact on patient treatment algorithms; specific therapies are needed to target these different mutations or changes in cellular morphology. For patients with the T790M mutation, there are currently no approved therapies. Several compounds that target the T790M mutation are in development. Second generation TKIs such as neratinib and afatinib have been shown to be more potent than erlotinib and gefitinib against the T790M mutation in vitro, but only at concentrations higher than the drug concentration required to maximally inhibit WT-EGFR.[24] Consequently, although there are several compounds in development, to date they have failed to demonstrate significant anti T790M activity in the clinic, likely because of dosing limitations caused by toxicity from WT-EGFR inhibition. Hence, patients who have progressed on first generation TKIs have limited treatment options. Assessment of post-progression survival in patients treated with EGFR TKI indicated patients with EGFR T790M-positive tumors had a median post progression survival of 1.9 years (95% confidence interval [CI], 1.6–2.6 years).[10] These patients are usually offered chemotherapy, which is known to cause increased toxicities compared with targeted therapies and does not offer a cure; progression eventually occurs. Thus, NSCLC patients who have failed treatment with TKIs and whose tumors express T790M mutation represent a group with fatal disease and unmet need.

In this patient population, CO-1686 was expected to provide improved activity by inhibiting a key resistance pathway. Furthermore, as CO-1686 has only minimal activity against WT EGFR, patients receiving CO-1686 may not experience the toxicities noted with first generation TKIs (eg, skin rash and diarrhea). In addition, this study aims to confirm and extend in a larger cohort of patients, early findings of activity in patients who test negative for the T790M mutation.

3.3 Nonclinical Overview

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

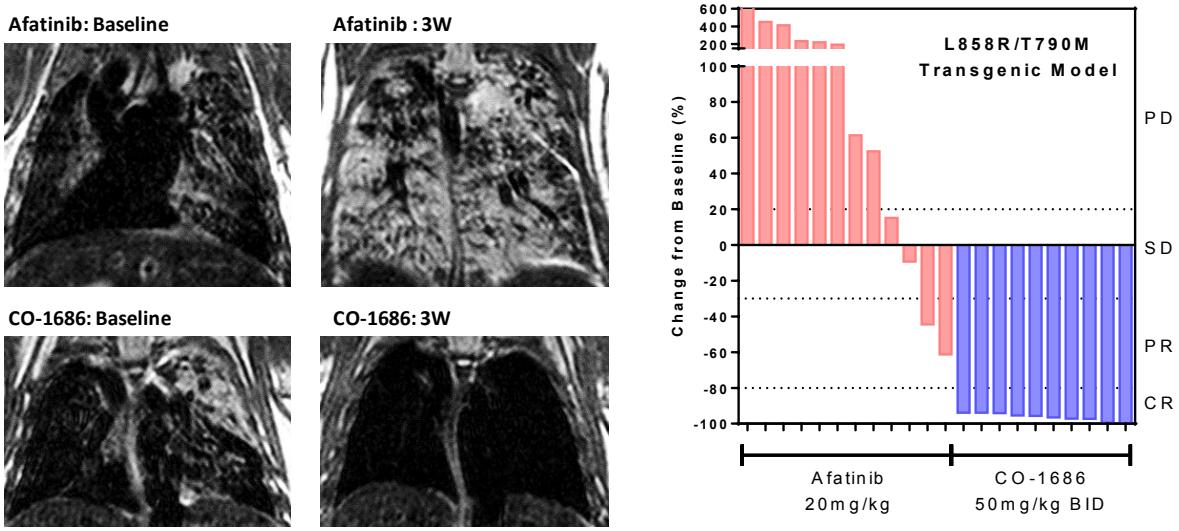
CO-1686 has been evaluated as a free base formulation (CO-1686 free base) and as a hydrobromide salt formulation (CO-1686 HBr). The pharmacologically active moiety, irrespective of formulation, is CO-1686.

Pharmacology

CO-1686 exhibits nonclinical antitumor activity as a single agent in cell lines expressing the most common activating and T790M EGFR mutations. The *in vitro* activity of CO-1686 was evaluated against common and rare lung-cancer associated EGFR mutants. CO-1686 was active against del19, L858R, G719S, an exon 19 insertion mutant, and L861Q, but not against an exon 20 insertion. Therefore, patients with exon 20 insertions have been excluded from participation in this study.

At clinically achievable doses CO-1686 shows potent activity in the NCI-H1975 ($EGFR^{L858R/T790M}$) and primary LUM1868 ($EGFR^{L858R/T790M}$) subcutaneous xenograft models.[25] 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, with very limited activity in the afatinib group (Figure 3-1).

Figure 3-1: CO-1686 Generates Complete Responses in L858R/T790M Transgenic Model



Metabolism

In 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 8.4 for further information). Caution should also be exercised in patients receiving PO 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*. Please see Section 8.3 for further information.

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 (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 four 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 gingival 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. There was no microscopic correlation associated with the redness of gingiva or lips.

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 Practices (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.

3.4 Clinical Experience with CO-1686

Five studies are currently ongoing in patients with advanced NSCLC (CO-1686-008, CO-1686-018, CO-1686-019, CO-1686-022, CO-1686-020).

Ongoing studies:

- CO-1686-008 (TIGER-X) is a 2-part, open-label, safety, pharmacokinetic (PK), and preliminary efficacy study of rociletinib in patients with advanced NSCLC. Part 1 is a Phase 1 dose escalation phase to determine the maximum tolerated dose (MTD) and is fully enrolled. The Phase 2 part of the study is the expansion portion in previously treated NSCLC patients who have documented evidence of an activating mutation in the EGFR gene and evidence of the T790M mutation based on prospective testing for T790M
- CO-1686-018 is a Phase 1, open-label, safety, PK, and preliminary efficacy study of rociletinib in Japanese patients with advanced NSCLC

- CO-1686-019 (TIGER-2) is a single arm, open-label, safety and efficacy study of rociletinib as second line EGFR-directed TKI therapy in patients with mutant EGFR NSCLC with the T790M mutation
- CO-1686-022 (TIGER-1) is a randomized, open-label, seemless phase 2/3 study evaluating the safety and efficacy of CO-1686 versus erlotinib in a first line setting in patients with advanced/metastatic NSCLC whose tumors have EGFR activating mutations
- CO-1686-020 (TIGER-3) is a randomized study evaluating the safety and efficacy of CO-1686 versus single agent chemotherapy in previously treated patients with mutant EGFR NSCLC

3.4.1 Safety

Please refer to the current version of Investigator's Brochure for the most up-to-date safety information.

Preliminary safety data are presented for the ongoing CO-1686-008 and completed CO-1686-016 studies. One hundred and ninety patients have received at least 1 dose of rociletinib as of 4 June 2014; 42 healthy male volunteers (Study CO-1686-016) and 148 patients with advanced NSCLC (Study CO-1686-008). The overall safety data presented here are for patients who received rociletinib in Study CO-1686-008 and included in the clinical database, as of the cut-off date of 4 June 2014.

3.4.1.1 Study CO-1686-008 - Ongoing Phase 1/2 Study

CO-1686-008 is an ongoing 2-part, open-label, safety, PK, and preliminary efficacy study of rociletinib in patients with advanced NSCLC. As of 4 June 2014, 148 patients with advanced NSCLC have received at least 1 dose of rociletinib. In the initial stage of the study, 57 patients were treated with rociletinib administered as CO-1686 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 rociletinib 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 had 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 (11% to 25%) across all rociletinib dose levels with the CO-1686 HBr formulation (500 mg BID, 625 mg BID, 750 mg BID, and 1000 mg BID). Hyperglycemia can be effectively managed with the addition of anti-hyperglycemic therapy and/or dose reductions. Guidance for the management of hyperglycemia associated with rociletinib treatment is provided in Section 7.4.

SERIOUS ADVERSE EVENTS (SAEs) AND DEATHS

A total of 43 patients experienced at least 1 SAE and 17 patients have reported an SAE assessed as related to study drug. Treatment-related SAEs are summarized in Table 3-1. The most commonly reported treatment-related SAE was hyperglycemia (reported in 6% of patients). Four patients (3%) experienced an SAE of vomiting and 3 patients (2%) experienced an SAE of nausea. All other treatment-related SAEs occurred in 2 or fewer patients.

To date, there have been 11 deaths while on study or within 28 days after the last dose of rociletinib. Eight deaths were reported as due to progression of NSCLC, 1 death due to pulmonary embolism, 1 death due to pneumonia, and 1 death of unknown cause. At this stage, a causal relationship with rociletinib cannot be ruled out for the death of unknown cause; all other deaths were reported as unrelated to study drug.

Table 3-1: Treatment-related Serious Adverse Events Reported in Patients in Study CO-1686-008

SOC PT	< 900 BID FB (N = 38)	900 BID FB (N = 19)	500 BID HBr (N = 18)	625 BID HBr (N = 17)	750 BID HBr (N = 50)	1000 BID HBr (N = 6)	Overall (N = 148)
Number of Patients with at Least 1 Treatment-related Treatment-emergent SAE							
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							
Combined terms of hyperglycemia	1 (2.6%)	0	4 (22.2%)	1 (5.9%)	2 (4.0%)	1 (16.7%)	9 (6.1%)
Decreased appetite	0	1 (5.3%)	0	0	0	0	1 (0.7%)
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: BID, twice daily; ECG, electrocardiogram; FB, CO-1686 free base; HBr, CO-1686 hydrobromide; N, number of patients; PT, preferred term; SAE, serious adverse event; SOC, system organ class.

Treatment-related Adverse Events (AEs)

Of the 148 patients treated with rociletinib as of the data cut-off date, 124 patients (84%) had at least 1 AE and 111 patients (75%) had an AE considered to be possibly, probably, or definitely related to rociletinib.

The most frequently reported AEs (≥ 20% of patients), regardless of causality or severity, were nausea (40%); AEs associated with blood glucose increases (39%; including Medical Dictionary for Regulatory Activities [MedDRA] preferred terms [PTs] blood glucose elevated, glucose tolerance impaired, and hyperglycemia); fatigue (26%); diarrhea (26%); and decreased appetite (22%).

AEs considered to be related to rociletinib and reported in > 5% of patients overall are summarized by system organ class (SOC), PT, and dose level in Table 3-2. The most frequently reported treatment-related AEs (≥ 20% of patients), regardless of severity, were nausea (28%); increased blood glucose, combined terms as in the previous paragraph (33%), and fatigue (20%).

The majority of AEs have been mild or moderate in severity. Rociletinib selectively inhibits mutant EGFR, and as expected, the syndrome of 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 6 patients [4%]) and all events were mild. In Study CO-1686 008, only 1 report of dermatitis acneiform and 1 report of follicular rash have been reported to date.

There have been 2 AEs of pneumonitis and 1 SAE of pneumonitis, all assessed as related to rociletinib by the investigator. Patients recovered after steroid therapy, and patients were not rechallenged with rociletinib.

Electrocardiogram (ECG) Changes

Rociletinib exposure is associated with QT interval corrected for heart rate (QT_C) prolongation. The effect takes several days to develop, and is not seen on Day 1 of therapy. Patients with low baseline resting heart rates appear to be at a higher risk for QT_C prolongation during treatment with rociletinib. Typically, the abnormality is evident by Day 15 of therapy, and the increase remains stable with continued dosing.

Prolonged QT_C is managed effectively by dose reduction.

Table 3-2: Treatment-related Adverse Events Reported in at Least 5% of Patients in Study CO-1686-008

SOC PT	< 900 BID FB (N = 38)	900 BID FB (N = 19)	500 BID HBr (N = 18)	625 BID HBr (N = 17)	750 BID HBr (N = 50)	1000 BID HBr (N = 6)	Overall (N = 148)
Number of Patients with at Least 1 Treatment-related TEAE							
Overall	**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 Administration 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							
Electrocardiogram QT prolonged	0	2 (10.5%)	0	2 (11.8%)	5 (10.0%)	3 (50.0%)	12 (8.1%)
Metabolism and Nutrition Disorders							
Combined terms of 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%)

Abbreviations: TEAE, treatment-emergent adverse event; BID, twice daily; FB, CO-1686 free base; HBr, CO-1686 hydrobromide; N, number of patients; PT, preferred term; SOC, system organ class.

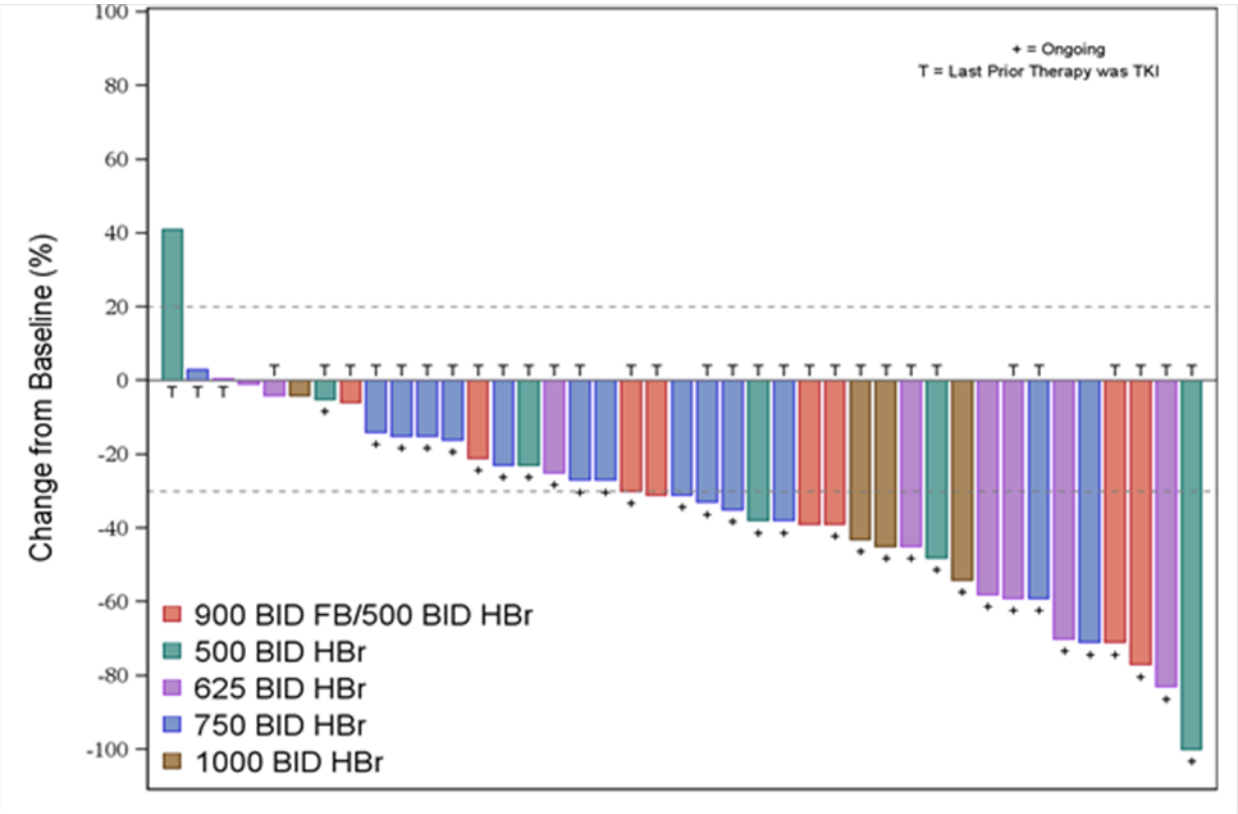
3.4.2 Activity of CO-1686

Please refer to the current version of Investigator's Brochure for the most up-to-date efficacy information.

CO-1686-008 is a 2-part, open-label, safety, PK, and preliminary efficacy study of rociletinib 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 rociletinib, encouraging signals of activity have been observed in an EGFR mutation positive patient population previously treated with one or more lines of an EGFR-TKI (eg, erlotinib, gefitinib, afatinib) and chemotherapy. A preliminary analysis of efficacy has been conducted using objective response rate (ORR), DR, and PFS as efficacy parameters. There is robust evidence of activity for rociletinib across the therapeutic doses (Figure 3-2) for patients confirmed as T790M-positive by central testing, with 22 of 40 patients achieving a Response Evaluation Criteria In Solid Tumors (RECIST) partial response (PR) as of the data cut-off date (Table 3-3). The ORR in this group of patients is 55% and the disease control rate (DCR) is approximately 92%.

Figure 3-2: Target Lesion Response in Centrally Confirmed T790M-positive Patients



Abbreviations: BID, twice daily; FB, CO-1686 free base; HBr, CO-1686 hydrobromide; T, last prior therapy was a tyrosine kinase inhibitor; +, ongoing.

Table 3-3: Best Response, Objective Response, and Disease Control Rate in T790M-positive 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						
PR	6 (75.0%)	3 (50.0%)	5 (55.6%)	5 (38.5%)	3 (75.0%)	22 (55%)
SD	2 (25.0%)	2 (33.3%)	2 (22.2%)	8 (61.5%)	1 (25.0%)	15 (45.5%)
PD	0 (0.0%)	1 (16.7%)	2 (22.2%)	0 (0.0%)	0 (0.0%)	3 (9.0%)
Objective Response (CR, PR)	6 (75.0%)	3 (50.0%)	5 (55.6%)	5 (38.5%)	3 (75.0%)	22 (55%)
Disease Control Rate (CR, PR, SD)	8 (100.0%)	5 (83.3%)	7 (77.8%)	13 (100.0%)	4 (100.0%)	37 (92.5%)

Data shown are for patients with measurable disease at baseline.
Abbreviations: BID, twice daily; CR, complete response; FB, CO-1686 free base; HBr, CO-1686 hydrobromide; N, number of patients; PR, partial response; SD, stable disease; PD, progressive disease.

In a recent interim analysis of patients receiving the therapeutically active doses of 500 mg BID and 625 mg BID, a response rate of 36% was achieved in a small subset (n = 11) of evaluable T790M-negative patients, with at least a Cycle 2 scan measurement (Soria 2014). These data demonstrate a signal of activity in patients with T790M-negative disease. Response rate and PFS in the T790M-negative group are longer than would be expected for single-agent cytotoxic chemotherapy in relapsed disease in an unselected population (data specific to T790M-negative patients are not available). Response rates of less than 10% with PFS under 3 months have been described for pemetrexed and docetaxel monotherapy (Alimta® label).

Rociletinib activity in T790M-negative patients could be explained by several factors including heterogeneous clones of cells within the tumor, with only T790M-negative clones captured within the biopsy sample, or a small fraction of T790M-positive cells falling out with the sensitivity limit of the assay.

The data support the inclusion of T790M-negative patients in clinical studies, to characterize the signal further.

3.4.3 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 CO-1686 HBr (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 3-12 hours postdose with a mean increase of 172% at C_{12h} (–22% to +400%) and a mean increase of 77% in

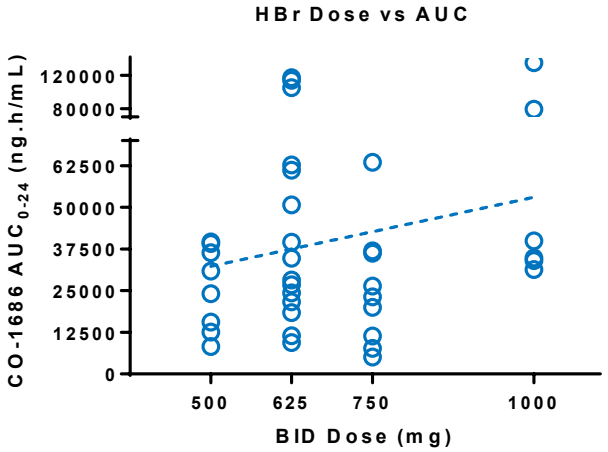
$AUC_{0–24}$ (+10% to 146%) with no change in elimination half-life ($T_{1/2}$); a slight mean increase of 12% in C_{max} was observed and a delayed time to C_{max} (T_{max}) was seen in a majority of subjects.

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 dosings 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 data following CO-1686 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 CO-1686 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 – 4.7 hours. 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 3-3).

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



3.5 Rationale for Study

There are limited treatment options for mutant EGFR NSCLC patients who have failed treatment with first generation TKIs and have acquired resistance through the T790M mutation. Currently there are no targeted therapies for these patients, who are usually treated with cytotoxic chemotherapy that has limited efficacy, but significant toxicity, in the second or third-line setting. Consequently, these patients represent a group with fatal disease and unmet need.

With potent nonclinical activity against activating EGFR mutations and the T790M resistance mutation, minimal inhibitory activity towards the WT, and with activity in clinical studies in both T790M-positive and T790M-negative populations, rociletinib may provide a tolerable and effective therapy for a patient population with few alternative treatment options.

In this study, the safety and efficacy of CO-1686 will be investigated in patients with mutant EGFR NSCLC who have progressed on their first single-agent EGFR-directed TKI and have a T790M-positive tumor (Cohort A).

An additional secondary goal will be to determine the effectiveness of CO-1686 in patients who test negative with respect to the T790M mutation, given initial findings suggestive of a clinical benefit of CO-1686 in this group of patients (Cohort B).

The therapeutically active doses of 625 mg BID and 500 mg BID will be investigated. Continuation of the ongoing Phase 2 program will obtain additional data at 500 mg BID to further describe the risk/benefit profile of CO-1686 across the therapeutic dose range.

4 STUDY OBJECTIVES AND ENDPOINTS

4.1 Objectives

4.1.1 Primary Objective

- To evaluate the antitumor efficacy of PO single-agent CO-1686, as measured by ORR, when administered to patients with EGFR-mutated, centrally confirmed T790M-positive and T790M-negative advanced NSCLC after tumor progression on 1 previous EGFR-directed TKI

4.1.2 Secondary Objectives

- To assess clinical efficacy in patients with centrally confirmed T790M-positive NSCLC: DCR, DR, PFS, and OS following CO-1686 treatment
- To assess quality of life (QoL) by patient-reported outcomes (PRO) following CO-1686 treatment
- To evaluate the safety and tolerability of CO-1686
- To determine the PK of CO-1686 using population PK (POPPK) methods and explore correlations between PK, exposure, response, and/or safety findings

4.1.3 Exploratory Objectives

- To evaluate clinical benefit of continued CO-1686 treatment following disease progression
- To evaluate concordance of mutant EGFR detection between tissue and plasma and assess CO-1686 mediated alterations in mutant EGFR levels over time using circulating tumor deoxyribonucleic acid (ctDNA) obtained from plasma
- To explore tissue and blood-based biomarkers that may be predictive of response or primary resistance to CO-1686 and investigate mechanisms of acquired resistance in the tissue and blood of patients who experience clinical progression during treatment with CO-1686

4.2 Endpoints

4.2.1 Primary Endpoint

- ORR according to RECIST Version 1.1.[11] For Cohort A, ORR will undergo independent radiology review (IRR) and in Cohort B, scans will be assessed by IRR if needed as a supporting analysis.

4.2.2 Secondary Endpoints

- DR, DCR and PFS according to RECIST Version 1.1 as determined by IRR
- ORR, DR, DCR and PFS according to RECIST Version 1.1 as determined by investigator assessment
- OS

- Change from baseline in PRO using the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30), EORTC Quality of Life Questionnaire Lung Cancer module (EORTC QLQ-LC13), and the Dermatology Life Quality Index (DLQI)[12,13]
- Treatment-emergent AEs, laboratory abnormalities and ECG abnormalities
- Plasma PK parameters for CO-1686 based on sparse sampling

4.2.3 Exploratory Endpoints

- Time-to-treatment failure
- Extra-cranial PFS
- Change from baseline in mutant EGFR levels in ctDNA obtained from plasma
- Positive and negative percent agreement between blood and tissue results for T790M
- Identify biomarkers associated with response or resistance to CO-1686

5 STUDY DESIGN

5.1 Overall Study Design and Plan

This is a Phase 2, single arm, open-label, dual cohort, multicenter study evaluating the safety and efficacy of CO-1686 administered PO BID to patients with previously-treated mutant EGFR NSCLC.

Patients will be enrolled into 2 cohorts. Cohort A will enroll approximately 125 eligible patients who are centrally confirmed T790M-positive and will be treated at 625 mg BID. Cohort B will be a continuation of the study and will enroll up to approximately 100 eligible patients who will be either centrally confirmed T790M-positive or T790M-negative. All patients in Cohort B will be treated at a starting dose of 500 mg BID. The priority for study enrollment will be for all T790M-positive patients to be enrolled into Cohort A first. Once Cohort A is complete, eligible T790M-positive patients will then be enrolled into Cohort B. All eligible T790M-negative patients will be enrolled into Cohort B.

All patients (for Cohort A and B) should have experienced disease progression while on treatment with the first single-agent EGFR-directed TKI (EGFR-TKI) therapy for advanced/metastatic NSCLC, and have had no intervening chemotherapy between EGFR-TKI and planned treatment with CO-1686. One line of chemotherapy prior to any EGFR-TKI treatment is permissible. The central laboratory will confirm that the patient's tumor harbors or does not harbor the T790M mutation using biopsy material obtained from either primary or metastatic tumor tissue within 60 days prior to dosing with study drug but after progression on EGFR-directed therapy.

5.1.1 Screening Period

Patients will undergo Screening assessments within 28 days before receiving the first dose of CO-1686. Patients will be monitored for AEs from the time the first dose of CO-1686 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 will also be collected. If a biopsy was performed within 60 days prior to Cycle 1 Day 1 (C1D1), and no intervening treatment was given, a repeat biopsy is not required if adequate tumor tissue can be provided to the sponsor during the Screening period.

5.1.2 Treatment Period

CO-1686 will be administered to patients BID (see Section 7.3). Patients will take CO-1686 with a meal or within 30 minutes after a meal. Treatment with CO-1686 is continuous, except where delayed or reduced according to protocol-specified toxicity criteria (Section 7.4). Each 28-day period of treatment will represent 1 cycle, with dosing initiated on C1D1. No dose escalation beyond the starting dose is allowed in either cohort. The counting of all 28-day cycles should start from C1D1.

Patients will undergo serial assessments for anti-tumor efficacy, drug safety, and PRO. Sparse blood sampling for POPPK analyses will be conducted in all patients treated with CO-1686. Serial blood sampling for longitudinal quantitative assessment of ctDNA will be conducted.

Tumor scans will be acquired by the investigative site and evaluated locally for patient treatment decisions; however, copies of all tumor scans will be sent to a central radiological vendor. In Cohort A, scans will be assessed by IRR for the primary endpoint evaluation. In Cohort B, scans will be assessed by IRR if needed as a supporting analysis. Protocol-specified treatment will continue until there is RECIST version 1.1 or clinical tumor progression or unacceptable toxicity as assessed by the investigator. Following disease progression on CO-1686 and discontinuation of protocol-specified treatment, patients who provide additional consent will undergo tumor biopsy before subsequent-line therapy is initiated. After discontinuation of protocol-specified treatment, subsequent anticancer therapy will be recorded.

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,[14] if the patient provides additional consent, and the investigator believes it is in the best interest of the patient, in consideration of the potential risks and benefits. The investigator should inform the sponsor of their decision prior to starting post-progression treatment. 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, and approved by, the sponsor and will be reviewed on a case-by-case basis. If a patient continues treatment post-progression, all study assessments including efficacy assessments, safety assessments, QoL administration, and blood collection for biomarker analysis and companion diagnostic development should continue per protocol. The patient should be discontinued from treatment once it is clear that no further clinical benefit can be achieved.

5.1.3 End-of-treatment

All patients should return to the clinic for end-of-treatment assessments 28 (± 7) days after the last dose of PO CO-1686 has been administered.

The trial will be completed when all enrolled patients have discontinued treatment in this protocol and completed the End-of-Treatment follow-up Visit.

5.1.4 Two Monthly Follow-up

After the End-of-Treatment Visit, all patients will be followed at approximately 2 monthly intervals to monitor disease progression (if patient discontinues treatment before progression), survival status, and subsequent NSCLC cancer therapy until death or sponsor decision, whichever comes first. After discontinuation of protocol-specified treatment, subsequent anticancer therapy use will be recorded.

5.1.5 Extension Phase

In mid-2015, Clovis submitted a New Drug Application for the use of rociletinib in patients with T790M-positive NSCLC. In June 2016, the FDA issued a Complete Response Letter to Clovis stating that more data is required to approve rociletinib 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.

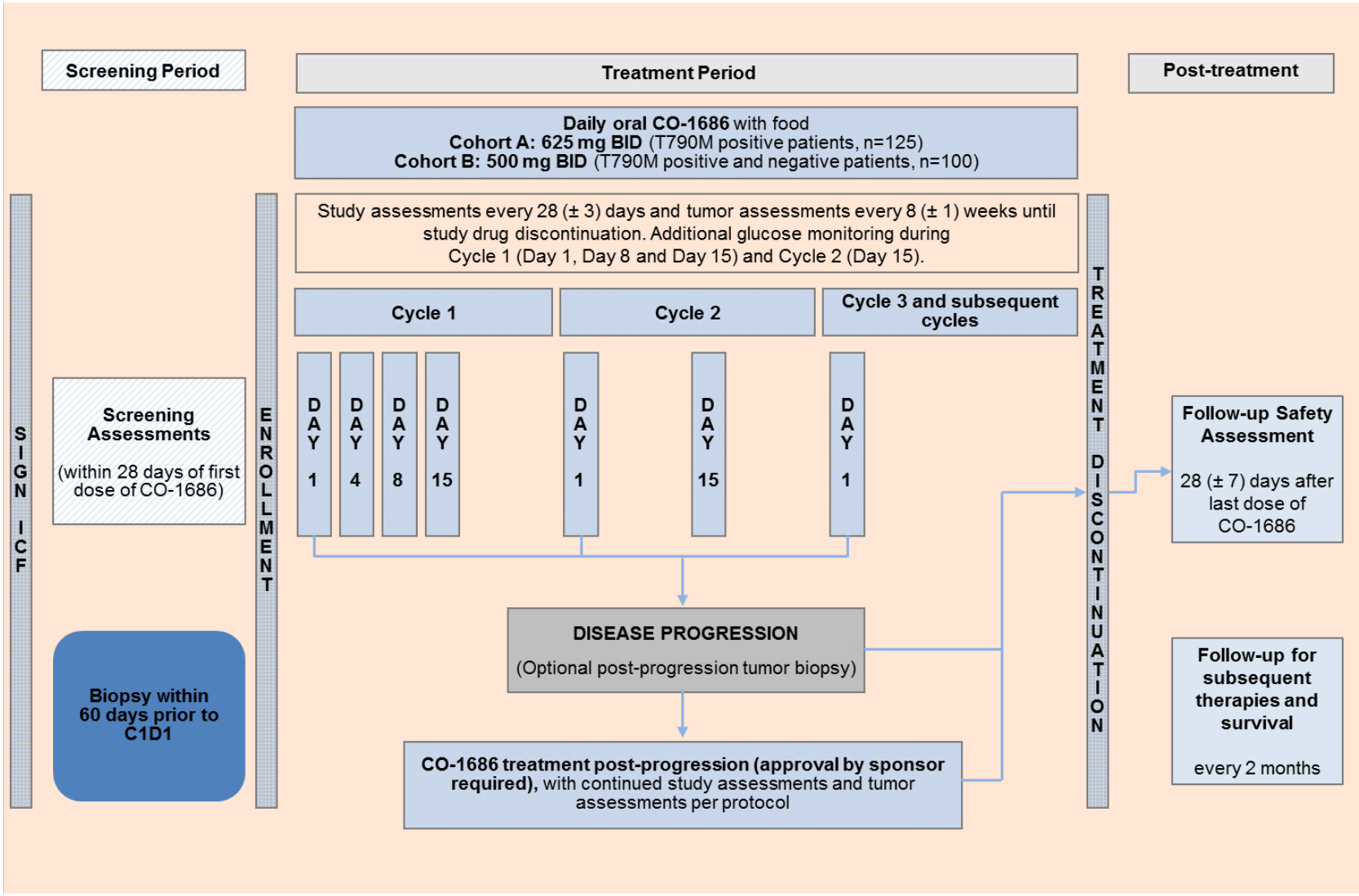
The purpose of this protocol amendment is to add a new Extension Phase to allow patients to continue on study but to avoid unnecessary collection of data that will no longer be analyzed or required for regulatory purposes, whilst maintaining an appropriate level of safety monitoring. A new schedule of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

For patients who wish to continue rociletinib treatment post progression, it is imporatant that a full exploration of alternative treatment options between patients and their treating physicians takes place.

5.2 Study Schema

The study schema in Figure 5-1 summarizes the treatment design of the study.

Figure 5-1: Study Schema



6 STUDY POPULATION

6.1 Number of Patients and Sites

The total enrollment planned for this study is approximately 225 patients. Patients will be enrolled into 2 cohorts:

Cohort A: Approximately 125 patients with centrally confirmed T790M-positive NSCLC will be enrolled. These patients will be treated at a dose of 625 mg BID.

Cohort B: Approximately 100 patients will be enrolled in order to include approximately 40 response evaluable, centrally confirmed T790M-negative patients. All Cohort B patients will be treated at a dose of 500 mg BID.

The priority for study inclusion will be for all T790M-positive patients to be enrolled into Cohort A first. Once this cohort is complete, eligible T790M-positive patients will then be enrolled into Cohort B. All eligible T790M-negative patients will be enrolled into Cohort B.

There will be approximately 90 investigative sites in the United States (US), Europe, Asia, and Australia.

6.2 Inclusion Criteria

All patients must meet all of the following inclusion criteria (both Cohort A and B, except where otherwise specified):

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

2. Documented evidence of a tumor with 1 or more EGFR mutations excluding exon 20 insertion

    - Disease progression confirmed by radiologic assessment while receiving treatment with the first single-agent EGFR-TKI (eg, erlotinib, gefitinib, afatinib, or dacomitinib)
        - EGFR-TKI treatment discontinued ≤ 30 days prior to planned initiation of CO-1686 (the washout period for an EGFR inhibitor is a minimum of 3 days)
        - No intervening treatment between cessation of single-agent EGFR-TKI and planned initiation of CO-1686
        - Previous treatment with ≤ 1 prior chemotherapy (excluding prior neo-adjuvant or adjuvant chemotherapy or chemoradiotherapy with curative intent)
        - Any toxicity related to prior EGFR inhibitor treatment must have resolved to Grade 1 or less
    - Central laboratory confirmation of the presence of the T790M mutation in tumor tissue in Cohort A and the presence or absence of the T790M mutation in tumor

tissue in Cohort B. Centrally indeterminate, unknown or invalid specimens are not acceptable. Biopsy material obtained from either primary or metastatic tumor tissue must have been obtained (and sent to the central laboratory) within 60 days prior to dosing study drug but following disease progression on the first EGFR-TKI.

3. Measureable disease according to RECIST Version 1.1

4. Life expectancy of at least 3 months

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

6. Age ≥ 18 years (in certain territories, the minimum age requirement may be higher eg, age ≥ 20 years in Japan and Taiwan)

7. 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
    - Renal Function
        - Serum creatinine ≤ 1.5 × ULN
    - Electrolytes
        - Potassium and magnesium within normal range. Patients may receive supplements to meet this requirement

8. Written 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 (both Cohort A and B, except where otherwise specified):

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

2. 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, with no evidence of that cancer currently, are permitted to enroll in the trial provided all chemotherapy was completed > 6 months prior and/or bone marrow transplant > 2 years prior
3. Known pre-existing interstitial lung disease
4. **Cohort A only**: Patients with leptomeningeal carcinomatosis are excluded. Other central nervous system (CNS) metastases are only permitted if treated, asymptomatic, and stable (not requiring steroids for at least 4 weeks prior to the start of study treatment). **Cohort B only**: Patients with CNS metastases or leptomeningeal carcinomatosis are excluded.
5. Treatment with prohibited medications (eg, concurrent anticancer therapy including other chemotherapy, radiation, hormonal treatment [except corticosteroids and megesterol acetate], or immunotherapy) ≤ 14 days prior to treatment with CO-1686
6. Patients who are currently receiving treatment with any medications that have the potential to prolong the QT interval and the treatment cannot be either discontinued or switched to a different medication before starting CO-1686
    - see http://crediblemeds.org/ for a list of QT-prolonging medications (includes all medication under categories of Known, Possible and Conditional risk of Torsades de Pointes)
7. Prior treatment with CO-1686, or other drugs that target T790M-positive mutant EGFR with sparing of WT-EGFR eg, AZD9291, HM61713, TAS-121
8. Any of the following cardiac abnormalities or history:
    - Clinically significant abnormal 12-lead ECG, QT interval corrected using Fridericia's method ($QTcF$) > 450 msec
    - 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
9. Nonstudy-related surgical procedures ≤ 7 days prior to administration of CO-1686. In all cases, the patient must be sufficiently recovered and stable before treatment administration
10. Females who are pregnant or breastfeeding
11. Refusal to use adequate contraception for fertile patients (females and males) while on treatment and for 12 weeks after the last dose of CO-1686

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

13. 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 result within 3 days prior to administration of the first dose of CO-1686. If the serum pregnancy results are not available on C1D1, 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 electronic case report form (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. Adequate contraception is defined as double-barrier protection (i.e., condom plus spermicide in combination with either 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 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. This also applies to male patients whose partners become pregnant while the patient is on study or within the 12-week period after last dose of study drug.

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 Investigational Product

CO-1686 is provided as yellow, film-coated tablets for PO administration in 2 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 15-30 °C (59-86 °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 gross visual defects such as chips. Defective tablets should be returned to the study site.

7.2 Method of Assigning Patients to Treatment Groups

All patients enrolled in the study will receive PO CO-1686.

7.3 Preparation and Administration of Protocol-specified Treatment

CO-1686 will be administered at a dose of 625 mg BID (Cohort A) or 500 mg BID (Cohort B). Patients should take CO-1686 as directed by the treating physician. 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 PO 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 patient diary to the next scheduled visit for reconciliation by site personnel.

7.4 Dose Modifications of Protocol-specified Treatment

No dose escalation beyond the starting dose is allowed in either cohort.

Dose reduction steps are allowed for each patient, with the overall number of dose reduction steps at the investigator's discretion. Dose reduction should be in increments of 125 mg BID

with up to 2 dose reduction steps permitted in both cohorts. Any need for further dose reduction, or adjustment from a twice to 3 times daily (TID) dosing regimen should be discussed with the sponsor before implementing. If a TID regimen is used, the total daily dose should not exceed 1,125 mg (i.e. not more than 375 mg TID).

For Grade 3 or 4 hematologic and non-hematologic toxicities (except for nausea/vomiting, alopecia, QTc prolongation and hyperglycemia), the dose should be initially reduced by 125 mg BID (to 500 mg BID, if the starting dose was 625 mg BID; or to 375 mg BID, if the starting dose was 500 mg BID). Re-escalation of dose after resolution of AEs must be discussed with, and approved by the sponsor.

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, 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 QTcF

ECGs will be measured throughout the study as described in the protocol. Readings for QTcF prolongation will be based on the average seen in the ECGs for each time point. Patients are required to have within-normal-range potassium and magnesium at enrollment, and these electrolytes should be maintained within range during CO-1686 treatment, if necessary using supplementation. If QT_C prolongation of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)[15] version 4.03 Grade 3 are 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. 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 can be evaluated. 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 and vomiting, and 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 the 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 the 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 the maximum approved dose of the 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 once daily (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 the treating physician. If a 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 professional (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 the treating physician.

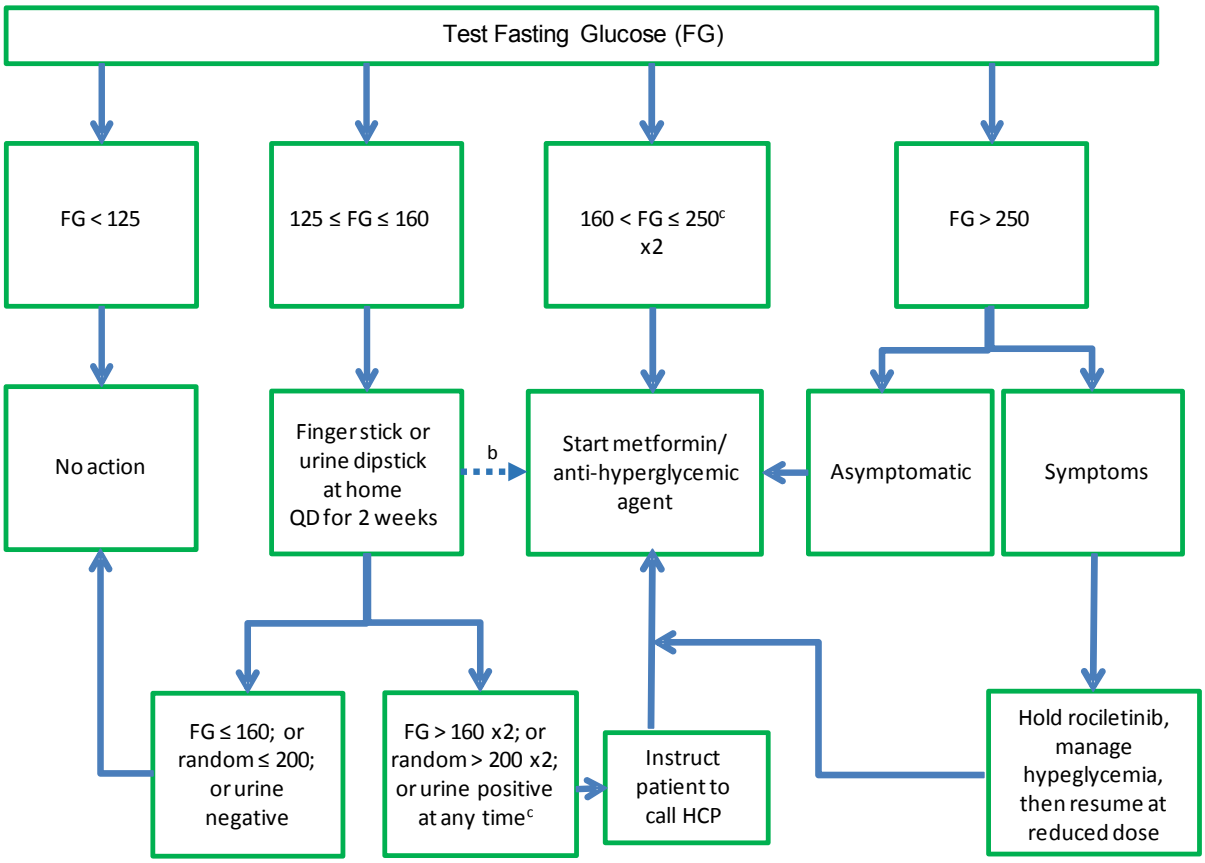
4. If fasting glucose > 250 mg/dL (> 13.87 mmol/L), and the patient is not symptomatic, manage as for Step 3 above. If the patient is symptomatic, then hold CO-1686 and bring glucose under control acutely, if necessary using insulin with conversion to metformin or anti-hyperglycemic agent of choice once 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 the 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 toxicity associated with metformin use, the extended release form and taking medication at bedtime are recommended to improve tolerability.[26] Additional recommendations to avoid gastrointestinal 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, increasing up to 1000 mg BID. If plasma glucose is not adequately controlled with the regimen outlined above, then consider adding pioglitazone or an SGLT-2 inhibitor and consider consultation with an endocrinologist.

End-of-treatment

When CO-1686 is discontinued, need and use of anti-diabetic medications should be reassessed and patient treated appropriately.

Figure 7-1: Guidelines for Management of Hyperglycemia



Abbreviations: FG = fasting plasma or serum glucose (in mg/dL); HCP = health care practitioner; QD = once daily.

[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.

[c] For patients with a single elevation, fasting glucose can be repeated at the next regularly scheduled assessment.

7.5 Accountability of Protocol-specified Treatment

Study personnel will maintain accurate records of CO-1686 shipments/receipts, administration, and drug reconciliation. The study site is responsible for the return or destruction of CO-1686 as required. A drug management system will manage CO-1686 inventory at all sites. The system will be required to manage study treatment requests and shipments.

Any CO-1686 accidentally or deliberately destroyed must be accounted for. All bottles must be accounted for prior to their destruction at the study center. Unused bottles should be destroyed locally. If destruction at the site is not possible, supply should be returned to the drug depot. During the course of the study and at completion of the study, the number of bottles of CO-1686 shipped, destroyed, and returned must be reconciled.

7.6 Blinding/Masking of Treatment

This is an open-label study; the investigational product will not be blinded or masked. All patients enrolled will receive PO CO-1686.

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 days of 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 clinic visit days. Patients (or legally authorized representative) will be asked to record dosing information for PO CO-1686 taken at home in the patient diary and to bring the patient diary and all unused tablets with them to scheduled clinic 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 patient diary in the patient's medical record.

8 PRIOR AND CONCOMITANT THERAPIES

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 (eg, $5HT_3$ 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 and be documented accordingly.

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

8.1 Anticancer or Experimental Therapy

No other anti-cancer 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. Treatment should be held 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 benefit from treatment overall. See Section 5.1.2 for more details.

8.2 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.

8.3 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. Selection of an alternative concomitant medication with no or minimal enzyme inhibition potential is recommended.

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.

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

Caution should be exercised in patients receiving PO CO-1686 and requiring concomitant medication with warfarin (Coumadin), NSAIDs, or clopidogrel, as CO-1686 moderately inhibited CYP2C8, CYP2C9 and CYP2C19 activities *in vitro*.

8.4 P-gp Substrates, Inhibitors and Inducers

Because CO-1686 is a P-gp inhibitor *in vitro*, caution should be exercised in patients receiving PO 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 and ritonavir, quercetin, quinidine, ranolazine, and verapamil.

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.

8.5 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.

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.

Because CO-1686 is absorbed optimally in an acidic environment, proton pump inhibitors or H2 blockers should be used with caution. If gastric acid blockade is required, short acting antacids are preferred.

9 STUDY PROCEDURES

Table 9-1 summarizes the procedures and assessments to be performed for all patients. All procedures and assessments will be performed for patients in both Cohorts A and B of the study, except where otherwise specified.

All procedures and assessments are to be completed at the scheduled time point and cycles should be counted forward from C1D1 of PO CO-1686 treatment unless otherwise indicated.

Table 9-1: Schedule of Assessments

	Before Any Study Assessments	Screening	Treatment Period (Daily Dosing)[a]							Post-treatment	
Procedure[b]		**Day –28 to Day –1**	**Cycle 1 Day 1 (C1D1)**	**Cycle 1 Day 4 ± 1 Day**	**Cycle 1 Day 8 ± 1 Day**	**Cycle 1 Day 15 ± 1 Day**	**Cycle 2 Day 1 (28 ± 3 Days After C1D1)**	**Cycle 2 Day 15 ± 1 Day**	**Cycle 3 + Day 1 Every 28 ± 3 Days**	**End-of-treatment (EOT) 28 ± 7 Days After Last Dose**	**Follow-up Every 8 ± 1 Weeks After EOT**
Informed consent	X										
Medical/oncology history		X									
Physical examination including weight		X (including height)	X				X		X	X	
ECOG performance status		X	X				X		X	X	
Vital signs[c]		X	X				X		X	X	
Prior/concomitant medications and procedures including prior treatment for NSCLC		X	X				X		X	X	
Contraceptive counseling[d]		X								X	
Serum pregnancy test[e]		X								X	
Hematology, including reticulocytes[f]		X	X				X		X	X	
Fasting serum chemistry[g]		X	X				X		X	X	
Fasting glucose		X	X	X	X	X	X	X	X	X	
Urinalysis[h]		X									
Tumor assessments and scans, including brain imaging at Screening[i]		X							X (every 8 ±1 weeks from C3D1, etc)	X	X

Table 9-1: Schedule of Assessments *(Cont.)*

	Before Any Study Assessments	Screening	Treatment Period (Daily Dosing)[a]							Post-treatment	
Procedure[b]		**Day –28 to Day –1**	**Cycle 1 Day 1 (C1D1)**	**Cycle 1 Day 4 ± 1 Day**	**Cycle 1 Day 8 ± 1 Day**	**Cycle 1 Day 15 ± 1 Day**	**Cycle 2 Day 1 (28 ± 3 Days After C1D1)**	**Cycle 2 Day 15 ± 1 Day**	**Cycle 3 + Day 1 Every 28 ± 3 Days**	**End-of-treatment (EOT) 28 ± 7 Days After Last Dose**	**Follow-up Every 8 ± 1 Weeks After EOT**
Tumor/metastasis biopsy for T790M assessment at central laboratory[j]		X; up to 60 days prior to C1D1								X (optional consent required)	
Blood for biomarker/EGFR mutational testing and exploratory research[k]		X; up to 60 days prior to C1D1	X				X		X	X	
Blood for CYP evaluation (optional consent required)[l]			X								
Adverse events[m]		X	X			X	X		X	X	
CO-1686 dispensing/administration			X				X		X		
Patient diary[n]							X		X	X	
Triplicate ECG assessment[o]		X	X			X	X		X	X	
Blood for sparse PK sampling and AAG serum levels (Central Lab)							X (Cycle 2 to 7 inclusive only)		X (Cycle 2 to 7 inclusive only)		
Quality of life questionnaires[p]		X	X						X (Every 8 ±1 weeks from C3D1, etc; Every 12 ±1 weeks from C10D1, etc)	X	

Table 9-1: Schedule of Assessments *(Cont.)*

	Before Any Study Assessments	Screening	Treatment Period (Daily Dosing)[a]							Post-treatment	
Procedure[b]		**Day –28 to Day –1**	**Cycle 1 Day 1 (C1D1)**	**Cycle 1 Day 4 ± 1 Day**	**Cycle 1 Day 8 ± 1 Day**	**Cycle 1 Day 15 ± 1 Day**	**Cycle 2 Day 1 (28 ± 3 Days After C1D1)**	**Cycle 2 Day 15 ± 1 Day**	**Cycle 3 + Day 1 Every 28 ± 3 Days**	**End-of-treatment (EOT) 28 ± 7 Days After Last Dose**	**Follow-up Every 8 ± 1 Weeks After EOT**
Survival status										X	X
Subsequent therapies for NSCLC										X	X

AAG = alpha-1 acid glycoprotein; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST – aspartate aminotransferase; β-hCG = β subunit of hCG 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; HbA1c = hemoglobin A1c; MRI = magnetic resonance imaging; PET = positron emission tomography; RECIST = Response Evaluation Criteria in Solid Tumors; WBC = white blood cells.

[a] = CO-1686 will be administered BID at 625 mg BID (Cohort A) or 500 mg BID (Cohort B), with a meal or within 30 minutes after a meal.

[b] = Unless specified, procedure is completed at the scheduled time point and is synchronized with administration day of CO-1686.

[c] = Vital signs (after at least 5 min rest) taken predose on C1D1, and without reference to dose at every subsequent visit.

[d] = Patients are to continue using effective contraception for 12 weeks after last dose of CO-1686 and report any pregnancies during this period.

[e] = Serum ß-hCG (local labs) from women of childbearing potential within 3 days prior to C1D1. If the serum pregnancy test results are not available on C1D1, a urine pregnancy test can be performed on C1D1 to confirm that the patient is not pregnant prior to dosing.

[f] = Central Lab: Includes hemoglobin, hematocrit, WBC and differential (with ANC), platelet count, and reticulocyte count ≤ 14 days prior to the first day of dosing. Blood will be sent for analysis at a central lab, but must also be analyzed by a local lab to inform treatment decisions. Local hematology results must be reviewed by the investigator prior to start of CO-1686 administration. Additional tests may be performed at the investigator's discretion.

[g] = Central Lab: Includes total protein, albumin, creatinine, BUN or urea, total bilirubin, alkaline phosphatase, ALT, AST, glucose, sodium, potassium, magnesium, chloride, calcium, phosphorus, total cholesterol, and HbA1c ≤ 28 days prior to first day of dosing. Samples analyzed by a central lab, but may also be performed locally to inform treatment decisions. Glucose must be measured following an 8 hour fast (no food or liquid other than water), and 'fasting glucose only' visits on C1D4, C1D8, C1D15, C2D15 will be performed at local labs only (not sent to central lab). HbA1c will be measured every other cycle (Day 1 of Cycle 3, 5, 7 etc).

[h] = Includes dipstick for protein, glucose, blood, pH, and ketones. If findings are abnormal, a microscopic evaluation will be performed to assess abnormal findings.

Table 9-1: Schedule of Assessments *(Cont.)*

	Before Any Study Assessments	Screening	Treatment Period (Daily Dosing)[a]							Post-treatment	
Procedure[b]		**Day –28 to Day –1**	**Cycle 1 Day 1 (C1D1)**	**Cycle 1 Day 4 ± 1 Day**	**Cycle 1 Day 8 ± 1 Day**	**Cycle 1 Day 15 ± 1 Day**	**Cycle 2 Day 1 (28 ± 3 Days After C1D1)**	**Cycle 2 Day 15 ± 1 Day**	**Cycle 3 + Day 1 Every 28 ± 3 Days**	**End-of-treatment (EOT) 28 ± 7 Days After Last Dose**	**Follow-up Every 8 ± 1 Weeks After EOT**
[i] =	Tumor scans obtained within 28 days prior to C1D1, may be used as the baseline scans. Scans include the chest and abdomen (preferably CT scans) using the same methods throughout the study. Other studies (MRI, X-ray) performed if required. Pelvic imaging should be performed if clinically indicated eg, prior or existing site of metastasis or symptomatic. Brain imaging (CT/MRI) is required at baseline. For Cohort A only, patients with brain lesions at baseline will require repeat brain imaging as part of the follow-up tumor assessments (patients with brain lesions at Screening are not eligible for Cohort B). Tumor scans will be performed during Screening and every 8 ± 1 weeks thereafter (Day 1 of Cycles 3, 5, 7 ± 1 week etc), until tumor progression, and at the EOT Visit (scans do not need to be repeated at EOT if < 2 weeks since last scan or patient had disease progression on study. An MRI may be used in place of a CT at EOT if required per local authorities. For patients with clinical progression, radiographic assessment should be performed to document evidence of radiographic progression. If a patient discontinues treatment before progression, then scans should continue until progression according to the protocol schedule. Exceptions to this requirement may be acceptable based on local institutional or regulatory requests and must be approved in advance by the sponsor. Patients who continue treatment with CO-1686 post-progression should continue scans every 8 ± 1 weeks until they discontinue treatment. Scans will be evaluated locally for patient treatment, with copies sent to a central radiological lab for independent evaluation (Cohort A) or for storage for later evaluation (Cohort B).										
[j] =	Central Lab: Biopsy tissue must be obtained within 60 days prior to C1D1 and following progression on the most recent therapy (extension of the 60-day window may only be allowed on a case by case basis, with sponsor approval). T790M assessment will be performed by a central lab to determine patient eligibility. At progression and/or EOT with CO-1686, an optional tumor biopsy will be performed with additional consent. All tissue processed locally as FFPE tissue.										
[k] =	Central Lab: Blood sampling for biomarker/EGFR mutational testing and exploratory research will be collected at Screening (prior to biopsy, or at least 2 days AFTER the biopsy was performed); pre-dose on C1D1, then at Day 1 of every subsequent cycle (every 28 ± 3 day intervals), and at the EOT Visit.										
[l] =	Central Lab: Blood for CYP evaluation to be collected pre-dose on C1D1 for patients who have signed optional consent										
[m] =	Patients will be monitored for AEs from the time the first dose of CO-1686 is administered through 28 days after the last dose. Study procedure-related AEs that occur after signing of the ICF and before administration of CO-1686 will also be collected.										
[n] =	Patient diaries should be collected and reviewed for compliance.										
[o] =	Taken in triplicate (> 2 min apart) anytime during Screening, pre-dose on C1D1, then at Day 1 of every subsequent cycle (every 28 ± 3 day intervals), C1D15, and at EOT, any time after treatment is discontinued										
[p] =	QoL Questionnaires (EORTC QLQ-C30, EORTC QLQ-L13, and the DLQI) will be collected at Screening, pre-dose on C1D1, then every 8 ± 1 weeks for the first 6 months (Day 1 of Cycles 3, 5, 7 ± 1 week inclusive). After Cycle 7, questionnaires will be collected every 12 ± 1 weeks (Day 1 of Cycle 10, 13, 16 ± 1 week etc) and at EOT.										

9.1 Screening Period

Following written informed consent, and unless otherwise specified, the following assessments should be performed during the 28-day period prior to the first dose (C1D1) of PO CO-1686 for Cohorts A and B, unless otherwise specified. If a biopsy was performed within 60 days prior to C1D1, and no intervening treatment was given, a repeat biopsy is not required if adequate tumor tissue can be provided to the sponsor during the Screening period.

Assessments performed prior to patient signing informed consent are acceptable only if confirmed to have been standard of care.

- Medical history, including demographic information (birth date, race, gender, etc.) smoking status, and oncology history including date of cancer diagnosis, prior cancer treatment, and any surgical procedures
- Documented evidence of a tumor with an EGFR mutation known to be associated with CO-1686 drug sensitivity (exon 19 deletion, L858R, G719X, L861Q, and S768I) and documentation of the presence of the T790M mutation in EGFR for Cohort A and the presence or absence of the T790M mutation in EGFR for Cohort B determined by NSCLC tumor tissue by the central laboratory (centrally indeterminate, unknown or invalid specimens are not acceptable; results can be documented > 28 days from C1D1 as biopsy can have occurred within 60 days prior to C1D1)
  - Biopsy material obtained from either primary or metastatic tumor tissue must have been obtained (and sent to the central laboratory) within 60 days prior to dosing study drug and following disease progression on the first EGFR-TKI. Extension of the 60-day window may only allowed on a case by case basis with sponsor approval.
  - Biopsy of primary or metastatic lesions to provide formalin-fixed paraffin-embedded (FFPE) tumor tissue for EGFR mutational testing and companion diagnostic kit development. To ensure adequate viable tumor tissue is obtained, image-guided biopsies should be achieved with 18- to 20-gauge cutting needles to ideally provide 1 to 3 cores measuring 1 to 1.5 cm in length. Tumor samples will be processed locally to yield FFPE tissue blocks. Entire FFPE blocks should be submitted, when possible. Blocks will be returned upon request if required for legal or medical treatment purposes.
  - If a biopsy was performed within 60 days prior to C1D1, and no intervening treatment was given, a repeat biopsy is not required if adequate tumor tissue can be provided to the sponsor during the Screening period
- Physical examination by body system, height, and weight
- ECOG performance status
- Vital signs (blood pressure, pulse, and temperature)
- Prior and concomitant medications and procedures (including prior treatment for NSCLC)
- Contraceptive counseling
- Serum pregnancy test (by local laboratory) within 3 days prior to the first day of dosing for women of childbearing potential. If the serum pregnancy test results are not available on

C1D1, 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.

- Hematology (hemoglobin, hematocrit, WBC and differential [with ANC], platelet count, and reticulocyte count) ≤ 14 days prior to the first day of dosing
  - **Fasting** serum chemistry (total protein, albumin, creatinine, blood urea nitrogen [BUN] or urea, total bilirubin, alkaline phosphatase, ALT, AST, glucose, sodium, potassium, magnesium, chloride, calcium, phosphorus, total cholesterol, and hemoglobin A1c [HbA1c])
- 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.
- Tumor assessments of the chest and abdomen. Pelvic imaging should be performed if clinically indicated eg, prior or existing site of metastasis or symptomatic. Assessments should consist of clinical examination and appropriate imaging techniques (preferably computed tomography [CT] scans with appropriate slice thickness per RECIST Version 1.1); other studies (magnetic resonance imaging [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.
- Blood sampling for biomarker/EGFR mutational testing and exploratory research that may lead to development of a plasma-based EGFR test, or that may be used for the development of a plasma-based EGFR test. Matched blood sampling (up to 25 mL at baseline and time of progression and up to 12 mL the beginning of every cycle) should be collected prior to the biopsy procedure, if possible. If blood sample is not collected before the biopsy, allow at least a 2-day recovery period after the biopsy before blood collection for biomarker testing. Detailed sample handling instructions are provided in the Laboratory Manual.
- AE monitoring (includes study procedure-related AEs that occur after signing of the ICF and before administration of CO-1686)
- 12-lead ECG (in triplicate, 10-sec tracings > 2 min apart)
- QoL questionnaires (EORTC QLQ-C30, EORTC QLQ-LC13, and the DLQI)

9.2 Treatment Period

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

Patients will take CO-1686 625 mg BID (Cohort A) or 500 mg BID (Cohort B), as directed. PO CO-1686 should be taken with 8 oz (240 mL) of water and with a meal or within 30 minutes after a meal. Patients will record the dose and timing of administration of PO CO-1686 in their daily dosing patient diary.

Unless otherwise specified, all patients in Cohorts A and B will undergo the following procedures and assessments. All procedures and assessments are to be completed at the

scheduled time point and the timing of all scans should be determined based on the date of C1D1 of PO CO-1686 treatment.

9.2.1 Cycle 1 Day 1 (C1D1)

Patients will be required to take their first dose at the clinic with 8 oz (240 mL) of water and with a meal or within 30 minutes after a meal.

To be performed *before* dosing:

- Physical examination
- Weight
- ECOG performance status
- Vital signs (blood pressure, pulse, and temperature)
- Concomitant medications and procedures
- Fasting serum chemistry (including fasting glucose)
- Hematology (including reticulocyte count)
- Blood sampling for biomarker/EGFR mutational testing and exploratory research
- Blood sampling for CYP testing (requires optional consent)
- AE monitoring
- CO-1686 tablets will be dispensed to the patient; patient diary will be provided to the patient
- 12-lead ECG (in triplicate, 10-sec tracings > 2 min apart) 5-10 minutes prior to dosing
- QoL Questionnaires (EORTC QLQ-C30, EORTC QLQ-LC13, and the DLQI)

To be performed *after* dosing:

- AE assessment
- Concomitant medications and procedures

9.2.2 Cycle 1 Day 4 (± 1 Day)

The following procedures will be performed at C1D4 (± 1 day):

- Fasting glucose (local laboratory)

9.2.3 Cycle 1 Day 8 (± 1 Day)

The following procedures will be performed at C1D8 (± 1 day):

- Fasting glucose (local laboratory)

9.2.4 Cycle 1 Day 15 (± 1 Day)

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

- Fasting glucose (local laboratory)
- 12-lead ECG (in triplicate, 10-sec tracings > 2 min apart)
- AE assessment

9.2.5 Cycle 2 Day 15 (± 1 Day)

- Fasting glucose (local laboratory)

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

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

- Physical examination
- Weight
- ECOG performance status
- Vital signs (blood pressure, pulse, and temperature)
- 12-lead ECG (in triplicate, 10-sec tracings > 2 min apart)
- 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).
- Blood sampling for biomarker/EGFR mutational testing and exploratory research
- Serum alpha-1 acid glycoprotein (AAG) samples and PK blood sample (Cycle 2 – 7 only; Section 9.5.3)
- Concomitant medication and procedures since last visit
- AE monitoring
- Collection and review of patient diary and CO-1686 drug return
- QoL questionnaires (EORTC QLQ-C30, EORTC QLQ-L13, and the DLQI) – at 8 ± 1 weeks for 6 months (Day 1 of Cycle 3, 5, 7, ±1 weeks inclusive). After Cycle 7, questionnaires will be collected every 12 ± 1 weeks (Day 1 of Cycle 10, 13, 16 etc ± 1 weeks) and at end-of-treatment
- CO-1686 tablets will be dispensed to the patient; patient diary will be provided to the patient
- Tumor assessments will be performed every 8 ± 1 weeks (Day 1 of Cycle 3, 5, 7 etc ± 1 week) after dosing until tumor progression (see Section 9.5.2.1).

9.3 End-of-Treatment Visit

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

- Physical examination
- Weight
- ECOG performance status
- Vital signs (blood pressure, pulse, and temperature)
- 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 (including fasting glucose)
- Tumor scans (using the same methodology as was used at Screening) unless it has been < 2 weeks since last scan or patient had disease progression on study. In addition, an MRI may be used in place of a CT at end-of-treatment scan if required per local authorities. For patients with clinical progression, radiographic assessment should be performed to document evidence of radiographic progression.
- Optional tumor biopsy (requires additional consent)
- Blood sampling for biomarker/EGFR mutational testing and exploratory research
- AE monitoring (until 28 days after last dose of PO CO-1686; then only ongoing SAEs will be followed until resolution or stabilization)
- Collection and review of patient diary and CO-1686 drug return
- 12-lead ECG (in triplicate, 10-sec tracings > 2 min apart)
- QoL questionnaires (EORTC QLQ-C30, EORTC QLQ-L13, and the DLQI)
- Survival status
- Subsequent therapies for NSCLC

9.4 Two Monthly Follow-up

The following procedures will be performed every 8 weeks ± 7 days (unless otherwise specified) following the End-of-Treatment Visit:

- Survival status - This may be performed during routine clinic visits or by telephone contact.
- Subsequent therapies for NSCLC will be documented during routine clinic visits or by telephone contact.

- If a patient discontinues treatment before progression, then scans should continue until progression according to the protocol schedule of every 8 ± 1 weeks. Exceptions to this requirement may be acceptable based on local institutional or regulatory requests and must be approved in advance by the sponsor.

9.5 Methods of Data Collection

9.5.1 Safety Evaluations

9.5.1.1 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 is administered through 28 days after the last dose. Study procedure-related AEs that occur after signing of the ICF and before administration of CO-1686 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.

9.5.1.2 Clinical Laboratory Investigations

Blood will be sent for analysis to a central laboratory for all cycles Day 1 visits, but must also be analyzed by a local laboratory to inform patient treatment decisions. Local hematology results must be reviewed by the investigator prior to start of CO-1686 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 evaluations 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 PO CO-1686.

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.

Fasting Glucose: 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 the End-of-Treatment Visit, also if clinically indicated on study. Fasting glucose will be measured as part of clinical chemistry panel (see below) on all cycles Day 1 visits, and measured individually (local lab) C1D4, C1D8, C1D15, and C2D15.

Clinical Chemistry: Total protein, albumin, creatinine, BUN or urea, total bilirubin, alkaline phosphatase, ALT, AST, total cholesterol, fasting glucose, sodium, potassium, magnesium, chloride, calcium, 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 Day 1 of 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.

Serum ß-hCG Pregnancy Test (Local Lab): Performed on women of childbearing potential within 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 on C1D1 to confirm that the patient is not pregnant prior to dosing. Both values should be entered in the eCRF. A negative result must be confirmed by a physician before the first dose of PO CO-1686 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.

9.5.1.3 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 minutes. Vital signs will be performed at Screening and at Day 1 of each cycle including the End-of-Treatment Visit.

9.5.1.4 12-lead Electrocardiograms

Triplicate serial 12-lead ECGs (10-sec ECG tracings collected in triplicate [> 2 min apart]) will be taken at Screening, C1D1, C1D15, C2D1, and every Cycle *N* D1, and 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 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.

9.5.1.5 Body Weight and Height

Height will be measured during the Screening visit only. Weight will be measured at Screening, at Day 1 of every cycle, and at the End-of-Treatment Visit (the patient should be in light indoor clothes).

9.5.1.6 Physical Examinations

Physical examinations will include an assessment of all the major body systems. Complete physical examinations will be performed at Screening, at Day 1 of every cycle, and at the End-of-Treatment Visit.

9.5.1.7 ECOG Performance Status

ECOG performance status (Appendix B) will be assessed at Screening, Day 1 of each cycle, 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.

9.5.2 Efficacy Evaluations

9.5.2.1 Tumor Assessments

Tumor assessments will be performed at Screening, and every 8 ± 1 weeks thereafter (Day 1 of Cycle 3, 5, 7 etc ± 1 week) until tumor progression, including at the End-of-Treatment Visit, if disease progression has not been documented previously. For patients with clinical progression, radiographic assessment should be performed to document evidence of radiographic progression. For a patient who discontinues treatment before progression, scans should continue until progression according to the protocol schedule. Exceptions to this requirement may be acceptable based on local institutional or regulatory requests and must be approved in advance by the sponsor. Scans will be evaluated locally for patient treatment decisions. Scans will be sent to a central radiological laboratory for independent response evaluation. In Cohort B, scans will be held at the central radiological vendor for later evaluation, assessed by IRR, if needed as a supporting analysis. Tumor response will be interpreted using RECIST Version 1.1 (Appendix A).[11]

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

Patients are required to have an end-of-treatment tumor scan using the same methodology used at Screening, **unless:**

a) Patient has radiographic evidence of disease progression while on study

or

b) It has been < 2 weeks since last on-study scan

In addition, an MRI may be used in place of CT at the end-of-treatment scan if required per local authorities.

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); other studies (MRI and X-ray) may be performed if required. Imaging of the pelvis is required if clinically indicated eg, prior site of metastasis or symptomatic. The same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study.

Brain imaging is required at baseline. In Cohort A, patients with brain lesions at baseline will require repeat brain imaging as part of the follow-up tumor assessments. In Cohort B, patients with brain lesions at Screening are not eligible for the study. Patients without baseline brain lesions do not require brain imaging on study unless clinically indicated.

9.5.3 Pharmacokinetic Evaluations

For all patients, 2 mL blood samples will be drawn for CO-1686 POPPK analysis at 28 ± 3 day intervals for the first 6 months (Day 1 of Cycles 2 to 7 inclusive). 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 levels and AAG measurement. Please refer to the laboratory manual for details on collection and processing of blood PK samples.

9.5.4 Biomarker Assessments

EGFR mutational status will be assessed in matching blood and tumor tissue collected at Screening from each patient. Tumor tissue from the primary tumor, or an accessible local/distal metastatic lesion, will be obtained during the Screening period or within 60 days prior to dosing. 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 FFPE tissue blocks. Entire FFPE blocks should be submitted when possible. Blocks will be returned upon request if required for legal or medical treatment purposes.

When sufficient tissue is available from the baseline tumor biopsy, samples will be tested for other molecular alterations including histological markers, EGFR gene amplification, MET gene amplification, or PIK3CA mutations that may modulate response or resistance to EGFR-targeted therapy.

Following disease progression on CO-1686, patients will undergo a tumor biopsy if they provide additional consent at that time. This tissue will be analyzed for molecular alterations that may confer resistance to EGFR inhibitors. Tissue preparation requirements are the same as listed above.

Matched blood sampling (up to 25 mL at baseline and time of progression and up to 12 mL the beginning of every cycle) should be collected prior to the biopsy procedure, if possible. If blood sample is not collected before the biopsy, allow at least a 2-day recovery period after the biopsy before blood collection for biomarker testing. Blood samples will be processed locally for plasma and stored frozen for subsequent batch shipping to the sponsor's lab.

- If a biopsy was performed within 60 days prior to C1D1, and no intervening treatment was given, a repeat biopsy is not required if adequate tumor tissue can be provided to the sponsor during the Screening period. Matched blood sampling should occur during the Screening period following signing of ICF.

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

For patients who provide additional consent, genomic DNA will be extracted from a blood sample from each patient (collected predose on C1D1) to detect genetic polymorphisms in CYP 450 isoenzymes in order to explore the correlation between potential polymorphisms and 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.

All patients (Cohorts A and B) will have blood collected during Screening, at Day 1 of each cycle, and at progression. Blood collected at these time points may also be used to test for biomarkers of response or resistance to EGFR-targeted therapy, including but not limited to EGFR mutational status, MET gene amplification, PIK3CA mutations, and alterations in other components of the EGFR signaling pathway.

Please refer to the Laboratory Manual for details on collecting and processing of blood pharmacodynamics samples.

9.5.5 Quality of Life Assessments

PRO will be measured using the EORTC QLQ-C30 and LC13 and the DLQI, which will be administered at Screening, predose on C1D1, then every 8 ± 1 weeks for 6 months (Day 1 of Cycle 3, 5, 7 ± 1 week inclusive). After Cycle 7, questionnaires will be collected every 12 ± 1 weeks (Day 1 of Cycle 10, 13, 16 etc. ± 1 week) and at end-of-treatment.

9.5.6 Patient Diary

Patient diaries will be provided to patients. Patients will use the diaries to note the date, time and dose of CO-1686 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 (eg, "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 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 PO CO-1686 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 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 (eg, respite care)
- Overdose of either Clovis study drug or concomitant medication unless the event meets SAE criteria (eg, 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 a 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 a 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

10.4 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 lab 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

10.5 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 10.8). **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.

10.6 Recording of Adverse Events and Serious Adverse Events

Any AE from the time the first dose of CO-1686 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 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 CO-1686, whether or not related to CO-1686, must be immediately reported to the sponsor/designee SAE contact (Section 10.8). After the 28-day window, only SAEs that are considered treatment-related should be reported to the sponsor/designee within 24 hours of knowledge of the event. SAEs that are not considered treatment-related should be reported per local institutional or regulatory policy and practices, using the SAE form until alternative therapy has started.

10.6.1 Intensity of Adverse Events

The severity of the AE will be graded according to the NCI CTCAE Version 4.03 grading scale. 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

10.6.2 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 (eg, 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

10.6.3 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
- Dose reduced/delayed
- CO-1686 temporarily interrupted
- CO-1686 permanently discontinued
- Other (specify)

Outcome

- Recovered
- Recovered with sequelae
- Improved
- Ongoing

- Death
- Lost to follow-up

10.7 Follow-up of Adverse Events and Serious Adverse Events

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 of CO-1686. All SAEs must be followed until resolution or stabilization.

10.8 Regulatory Aspects of Serious Adverse Event Reporting

All SAEs, 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 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 File.

Clovis 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 U.S. 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 (EC) 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), Clovis 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. Clovis 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:

Tumor Evaluable Population—all patients who received at least 1 dose of CO-1686, have at least 1 measureable tumor lesion at baseline, and have at least 1 post-baseline tumor assessment as determined by the IRR.

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

11.2 Statistical Methods

11.2.1 General Considerations

Data will be summarized by T790M status and by dose, but may also be pooled as appropriate.

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 PFS and OS.

All data will be used to their maximum possible extent but without any imputations for missing data.

All statistical analyses will be conducted with the statistical analysis software (SAS®) System.

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 will be summarized.

11.2.3 Baseline Characteristics

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

11.2.4 Efficacy Analyses

The efficacy endpoints will be evaluated using RECIST Version 1.1 for the tumor evaluable population. Separate analyses will be performed for the assessments from the investigator and the independent reviewer.

PFS and OS will also be presented for the safety population.

11.2.4.1 Primary Endpoint

The primary endpoint of the study will be ORR according to RECIST Version 1.1. For Cohort A, ORR will undergo independent radiology review (IRR) and in Cohort B, scans will be assessed by IRR if needed as a supporting analysis.

The ORR is the best overall response 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, SD, or progressive disease (PD) will be summarized.

11.2.4.2 Secondary Efficacy Endpoints

BEST OVERALL RESPONSE

The frequency and percentages of best overall responses of CR, PR, SD, or PD will be summarized separately for T790M-positive and T790M-negative patients, and by dose.

DURATION OF RESPONSE

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 separately for T790M-positive and T790M-negative patients, and by dose, 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.

DISEASE CONTROL RATE

DCR is defined as the percentage of patients who have achieved CR, PR, and SD lasting at least 12 weeks.

PROGRESSION-FREE SURVIVAL

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

For patients who continue treatment post-progression, the first date of progression will be used for the analysis of PFS.

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.

POPULATION PK ANALYSES

Sparse blood sampling for POPPK analyses will be conducted in all patients treated with CO-1686. A specific POPPK 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.

QUALITY OF LIFE

QoL will be measured using the EORTC QLQ-C30, EORTC QLQ-LC13, and the DLQI.[12,13]

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

Evaluation of Symptoms

An improvement in symptoms will be defined as a $\geq$ 10 point decrease from baseline. A worsening in symptoms will be defined as a $\geq$ 10 increase from baseline. Patients with neither an increase nor a decrease will be considered stable. The frequency and percentage of patients categorized as an increase, stable, or decrease will be presented.

Time to Deterioration

The time to a worsening in symptoms will be computed as 1+ the number of days from the first dose of study drug to the first instance of a $\geq$ 10 point increase from baseline in symptoms.

The time to deterioration will be summarized using Kaplan-Meier methodology. Patients without a 10 point increase will be censored on their last evaluation.

Longitudinal Analysis

The summary of QoL data will include descriptive statistics (N, mean, standard deviation, minimum, median, and maximum) of the mean and/or percent change from baseline during the on-treatment period. Summaries using descriptive statistics of the change from baseline to each scheduled visit during the on-treatment period will be presented.

Graphical presentations may be used to present the mean changes over time.

11.2.4.3 Exploratory Endpoints

TIME-TO-TREATMENT FAILURE

The time-to-treatment failure will be computed as 1+ the number of days from the first dose of study drug to the last dose of study drug and will be presented with summary statistics.

EXTRA-CRANIAL PFS

In the subgroup of patients with brain metastases at baseline, extra-cranial PFS will be calculated as 1+ the number of days from the first dose of study drug to a 20% increase from nadir in the sum of the longest diameters of the extra-cranial target lesions.

Patients without extra-cranial progression will be censored on the day of their last tumor assessment.

CIRCULATING TUMOR DNA (CTDNA)

The presence of both the activating mutation and T790M at baseline and subsequent time points will be presented both as copies/mL plasma and mutant allele percentages and summarized with descriptive statistics.

COMPARISON OF BLOOD AND TISSUE RESULTS FOR T790M

The relationship between T790M detected in tumor compared with that detected in blood will be explored. This will involve determining the sensitivity, specificity, and positive and negative predictive values of blood with respect to tumor assuming that EGFR mutational status in tumor is a true reflection of tumor biology.

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).

11.2.5.1 Extent of Exposure

The following will be summarized:

- Number of weeks of treatment initiated
- Number of dose reductions, delays or interruptions

The number of weeks of treatment initiated will be investigated by summarizing the number of weeks started by each patient. The number of patients with at least 1 dose reduction, delay or interruption will be summarized with frequencies and percentages.

11.2.5.2 Adverse Events

AE coding will be performed using MedDRA. The severity of the toxicities will be graded according to the NCI CTCAE v4.03 whenever possible. Treatment-emergent AEs are defined as

AEs with an onset date on or after the date of first dose of CO-1686 until the date of the last CO-1686 dose 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 SOC and PT will be presented. Multiple instances of the treatment-emergent AEs in each SOC and multiple occurrences of the same PT are counted only once per patient. The number and percentage of patients with at least 1treatment-emergent AE will also be summarized.

Separate tables will present the following:

- 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 PO CO-1686
- Treatment-emergent AEs resulting in interruption or reduction or delay of CO-1686

The incidence of treatment-emergent AEs will be summarized by relationship to PO CO-1686 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 PO CO-1686. The on-treatment period will be defined as the day after the first dose of PO CO-1686 to 28 days after the last dose of CO-1686. 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. 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. Separate listings will be produced for clinically significant laboratory abnormalities (i.e., those that meet Grade 3 or 4 criteria according to CTCAE).

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. The on-treatment period will be defined as the day after the first dose of CO-1686 to 28 days after the last dose of CO-1686. 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. 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.

11.2.5.5 12-lead Electrocardiograms

ECG intervals will be stratified into categories indicative of potential clinical significance. Each patient's maximum QT and QT_C intervals from the pretreatment visit and treatment period visits will be classified as ≤ 450 msec, > 450 msec to ≤ 480 msec, > 480 msec to ≤ 500 msec, and > 500 msec. For each patient's maximum change from the pretreatment ECG visit for QT and QT_C, intervals will be classified into < 30 msec, ≥ 30 msec to < 60 msec, and ≥ 60 msec. 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 will be provided.

11.2.5.6 Other Safety Measurements

Concomitant medications/procedures will be tabulated and summarized.

11.2.6 Exploratory Endpoints–Pharmacodynamic Analysis

An exploratory pharmacodynamic endpoint is the detection and quantification of mutant EGFR ctDNA in blood collected at baseline and with every tumor assessment. The presence of both the activating mutation and T790M at baseline and subsequent time points will be presented both as copies/mL plasma and mutant allele percentages. In addition, the relationship between T790M detected in tumor compared with that detected in blood will be explored. This will involve determining the sensitivity, specificity, positive and negative predictive values with 95% CIs of blood with respect to tumor assuming that EGFR mutational status in tumor is a true reflection of

tumor biology. The ctDNA from blood collected at these time points may also be assessed to identify biomarkers of response or resistance to EGFR-targeted therapy.

11.3 Sample Size Considerations

Cohort A: Approximately 125 patients will be enrolled. The ORR will be presented with 95% CIs. Table 11-1 provides the 95% CIs for observed response rates of 30%, 40%, and 50% assuming a total of 125 patients.

Table 11-1: Confidence Intervals for Observed Response Rates

Number of Patients	ORR (%) [95% CI]
125	30 [22, 39]
125	40 [31, 49]
125	50 [41, 59]

Cohort B: Approximately 100 patients will be enrolled with the aim to include approximately 40 response evaluable T790M-negative NSCLC patients. To be response evaluable, patients should have received at least one cycle of therapy, and have had their disease re-evaluated by radiological assessment.

An exact binomial test with a nominal 0.10 2-sided significance level will have approximately 90% power to detect the difference between a null hypothesis response rate of 20% and a clinically meaningful response rate of 40% when the sample size is 40.

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
- Progression of patient's underlying disease, except as noted in Section 5.1.2
- 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 PO CO-1686 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. The End-of-Treatment Visit should occur 28 (± 7) days following the last dose of CO-1686. 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 if the patient discontinues treatment prior to progression (every 8 ± 1 weeks until disease progression), and for survival status and subsequent NSCLC therapies (at approximately 2-monthly intervals until death or sponsor decision).

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 or equivalent 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 at 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.

Clovis 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 Clovis. 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, the eCRFs, 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.

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 Clovis 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 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 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, Clovis and the investigator will assure that adequate consideration is given to the protection of the patients' interests.

Clovis 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 PO 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 Clovis. 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 Clovis, 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 Clovis 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 Clovis. 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 Clovis. Should the investigator wish to assign the study records to another party or move them to another location, Clovis must be notified in writing of the new responsible person and/or the new location. Clovis 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 Clovis 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 Clovis and shall be held in strict confidence along with all information furnished by Clovis. 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 Clovis. Written permission to the investigator will be contingent on the review by Clovis of the statistical analysis and manuscript, and will provide for nondisclosure of Clovis 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 Clovis. 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

Appendix B. Eastern Cooperative Oncology Group Performance Status Scale

Appendix C. Study CO-1686-019 Extension Phase

Appendix A
Response Evaluation Criteria in Solid Tumors Criteria

The RECIST guidelines (Version 1.1) are described in Eisenhauer (2009)[11] 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 nonmeasurable).
3. A minimum size of 20 mm by chest X-ray.

All tumor measurements must be recorded n 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.

Nonmeasurable 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 nonmeasurable lesions, are considered nonmeasurable disease. Lesions considered truly nonmeasurable 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, 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 nonmeasurable.

Cystic Lesions

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) 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.

Nontarget 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 nontarget) 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 nontarget lesions and normalization of tumor marker level.
Stable Disease/Incomplete Response	Persistence of one or more nontarget 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 nontarget 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	**Nontarget 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; eg, 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 (fine needle aspiration/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 (eg, 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: Study CO-1686-019 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.

In addition, Amendment 5 also introduces the availability of NAT2 testing for patients, an indirect indicator of the likelihood of developing hyperglycemia 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.

INTRODUCTION

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 rociletinib 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. 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 C, Table 1, Appendix C, Table 2, and Appendix C, 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 C, 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 C, Table 2 shows that hyperglycemia appears to be less frequent and less severe in rapid acetylators. Appendix C, Table 3 shows that QTcF prolongation on ECG appears to be less frequent and less severe in rapid acetylators.

Appendix C, 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 C, 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 C, 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 (31%)	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 rociletinib 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 rociletinib whilst on treatment.

STUDY DESIGN

Treatment Regimen and Duration of Therapy

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.

Patients may continue to receive CO-1686 if the PI and patient deem it is appropriate for the patient though the availability and suitability of alternative treatment options should be considered by the treating physician and discussed with the patient. 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 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 rociletinib post progression, 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 CO-1686 treatment in the CO-1686-019 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 Investigatory and with the approval of the sponsor.
- Intercurrent illness that prevents administration of treatment (Reference Section 7.7)
- 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 C,Table 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.

Appendix C, Table 4. Schedule of Assessments – Extension Phase

	Prior to beginning Amendment 5 Evaluations	Day 1 of each cycle	End of Treatment (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
Fasting Serum Chemistry[d]		X	X
Hematology[e]		X	X
Adverse Events[f]		X	X
Patient Diary[g]		X	X
CO-1686 Dispensing / Administration		X	
ECG Assessments using central ECG machine[h]		X	X
Tumor Scans[i]	To be performed per institutional standard of care or every 8 ± 1 weeks (every 2 cycles); scans are not required at the End of Treatment Visit		
Blood for CYP Evaluation (Optional Sampling)[j]		X	

[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 and report any pregnancies during this period.
[c] = Serum ß-hCG to be evaluated by local lab and performed only on women of childbearing potential.
[d] = Glucose must be measured following an 8 hour fast (no food or liquid other than water). Hemoglobin A1c will be measured on Day 1 of every other cycle while the patient is on study.
[e] = Hematology evaluation should include reticulocytes.
[f] = Patients will be monitored for AEs from the time the first dose of CO-1686 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 QTc 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 laboratory 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 1 sample is needed and may be collected at any visit to enable NAT2 analysis.

Day 1 of Each Cycle

Patients will be instructed 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) using central ECG machine 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.
- 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
- Collection and review of patient diary and CO-1686 drug returnCO-1686 tablets will be dispensed to the patient; patient diary will be provided to the patient
    - Oral CO-1686 will be administered with a meal, or within 30 minutes after a meal. The patient must also drink at least 8 ounces (240 mL) of water when taking CO-1686. Tablets should be swallowed whole.
- 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:

- Physical examination
    - 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
- AE monitoring (until 28 days after last dose of oral CO-1686; then only ongoing serious adverse events (SAEs) are followed until resolution or stabilization)
- Collection and review of patient diary
- Contraceptive counseling