A Phase 1/2, Open-Label, Safety, Pharmacokinetic and Preliminary Efficacy Study of Oral CO-1686 in Patients with Previously Treated Mutant EGFR Non-small Cell Lung Cancer (NSCLC)

Protocol Number:	CO-1686-008
Investigational Product:	CO-1686
Eudra CT Number	[redacted]
IND Number:	[redacted]
Development Phase:	Phase 1/2
Indication Studied:	Locally advanced or metastatic NSCLC with mutant epidermal growth factor receptor (EGFR)
Sponsor Name and Address:	Clovis Oncology, Inc. 5500 Flatiron Parkway, Suite 100 Boulder, CO 80301 USA Phone Number: 303-625-5000 Facsimile Number: 303-245-0360
Responsible Medical Officer:	[redacted]
Compliance Statement:	This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, clinical research guidelines established by the Code of Federal Regulations (Title 21, CFR Parts 50, 56, and 312), and International Conference on Harmonization (ICH) Good Clinical Practices (GCP) Guidelines.. Essential study documents will be archived in accordance with applicable regulations.

[redacted]

CONFIDENTIALITY STATEMENT

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Protocol Approval Signature Page

Protocol: CO-1686-008

Title: A Phase 1/2, Open-Label, Safety, Pharmacokinetic and Preliminary Efficacy Study of Oral CO-1686 in Patients with Previously Treated Mutant EGFR Non-Small Cell Lung Cancer (NSCLC)

Date: August 03 2016

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Protocol Acceptance Form

Protocol: CO-1686-008

Title: A Phase 1/2, Open-Label, Safety, Pharmacokinetic and Preliminary Efficacy Study of Oral CO-1686 in Patients with Previously Treated Mutant EGFR Non-Small Cell Lung Cancer (NSCLC)

Date: August 03 2016

[redacted] [redacted]

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

Investigator's Signature _____ Date _____

Name (printed) _____

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1 SYNOPSIS

Protocol Number	CO-1686-008
Title	A Phase1/2, Open-Label, Safety, Pharmacokinetic, and Preliminary Efficacy Study of Oral CO-1686 in Patients with Previously Treated Mutant EGFR Non-Small Cell Lung Cancer (NSCLC)
Phase	Phase 1/2
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 are 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 the study at the discretion of the Principal Investigator in an extension phase. No further patients will be enrolled in this study. The purpose of this protocol amendment (Amendment 8) is to add a new Extension Phase to allow patients to continue on the study but to avoid unnecessary collection of data that will no longer be analyzed or required for regulatory purposes, whilst maintaining an appropriate level of safety monitoring. A new schedule of assessments for the Extension Phase as well as a complete description of procedures is provided in Appendix D. This schedule replaces all schedules of assessments in Section 9.1 and should be followed for all patients. In addition, Amendment 8 (Appendix D) 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 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 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 (del19), typically have good responses to therapy with first-generation EGFR inhibitors such as erlotinib or gefitinib.[2,3] Toxicity associated with both erlotinib and gefitinib includes skin-rash and diarrhea related to inhibition of the wild-type EGFR in skin and intestine, respectively.[4,5,6] Despite the impressive initial response to treatment, progression generally occurs after 9 to 14 months of erlotinib or gefitinib therapy, driven in approximately 50% of cases by a second site T790M mutation (the "gatekeeper" mutation) in exon 20 of EGFR that mediates resistance to first-generation EGFR inhibitors.[7,8]

	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 developed T790M-mediated resistance to first generation EGFR inhibitors. Toxicities driven by WT EGFR inhibition should be minimal in treated patients. The goals of this study are: (A) to evaluate the pharmacokinetic (PK) and safety profile of oral CO-1686; (B) to determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of oral CO-1686; (C) to assess the safety and efficacy of CO-1686 in previously treated NSCLC patients known to have the T790M EGFR mutation. CO-1686 was being developed with a companion diagnostic to identify patients whose tumors express activating EGFR mutations as well as the T790M resistance mutation. To evaluate alternative and less invasive procedures than tumor tissue biopsy to provide DNA, serial plasma samples from all patients will be analyzed for the presence of EGFR mutations including T790M in plasma. Patients will also have the option to provide serial urine specimens to determine whether EGFR mutations are detectable in transrenal nucleic acids.[9] The study was initiated in April 2012 using the free base form of CO-1686. Fifty-seven patients were treated with CO-1686 free base between April 2012 and August 2013. The highest dose of free-base CO-1686 administered was 900 mg BID; the MTD was not established. A hydrobromide (HBr) salt form of CO-1686 that has superior PK characteristics was introduced into the clinic in August 2013. CO-1686-HBr was tested at 500 mg BID, 625 mg BID, 750 mg BID, and 1000 mg BID in the dose escalation phase of the study. All doses tested had less than 33% incidence of dose limiting toxicities in Cycle 1. The dose of 750 mg BID was selected as suitable for further study and 2 expansion cohorts (Cohorts A and B) were opened at that dose level. Subsequently, as the Phase 1 data matured, the recommended dose was adjusted to 625 mg BID based on robust antitumor activity at lower doses and anticipated optimal tolerability. RECIST responses have been observed across the range of doses studied in Phase 1. The current overall response rate in patients with T790M+ NSCLC is approximately 60%, based on a data cut from 40 patients in this study for the FDA end of Phase 2 meeting held in July 2014. The most common Grade 3 toxicity observed is hyperglycemia, occurring in approximately 30% of patients, which is most often managed with oral hypoglycemic monotherapy. Protocol Amendment 6 added dose levels of 500 mg BID and 625 mg BID to the Phase 2 cohorts to perform a comprehensive evaluation of dose and response and tolerability across multiple dose levels (Cohorts A and B), as well as an additional cohort (Cohort C – 625 mg BID regimen) to accommodate patients with a positive local T790M result but discrepant or inadequate central result. In Amendment 6, patients were to be allocated to the 500 mg or 625 mg BID regimens by 1:1 randomization.

	Amendment 7 made the following changes: 1. Clarification of CNS lesion exclusion criterion to ensure only patients with stable CNS disease are enrolled 2. Removal of the requirement for 1:1 randomization to the 2 dose levels. This will allow additional early experience to be gained at the recommended dose (625 mg BID) in order to support the Phase 2/3 program where studies are enrolling at 625 mg BID, as well as regulatory filings. 3. Allowing for a potential increase in the size of Cohort A. Experience to date shows that Cohort A (later line patients) enrolls more rapidly than Cohort B (second line patients). Amendment 7 allows enrolment to continue in Cohort A until Cohort B is fully enrolled. Based on current enrollment rates, the size of Cohort A will increase from 150 patients to approximately 275 patients. 4. Clarification that removal of 1:1 randomization allows patients to enroll in study before the central T790M status is obtained, in cases where the following conditions are met: a. Have undergone a biopsy of either primary or metastatic tumor tissue within 60 days of dosing with study drug and have tissue available to send to the sponsor's lab or are able to undergo a biopsy during screening. No change (except for washout or dose adjustment if required to manage adverse effects) in antitumor therapy regimen is allowed between the biopsy and CO-1686 initiation (Study Inclusion Criterion 3); AND b. Local positive T790M result from biopsy taken at same time as central testing biopsy, with results available for sponsor review before enrollment 5. Clarification of requirements for continued treatment of patients who progress on CO-1686.
Study Overview	This study will include 2 parts: • Phase 1: Dose-escalation Period with 21-day cycles; optional Treatment Extension Period starting on Day 22 • Phase 2: Evaluation of activity and safety in patients with the T790M EGFR mutation who have: **Cohort A** – Progressed on EGFR directed therapy (irrespective of the number and order of previous lines of NSCLC therapy) (Dose levels of 750 mg BID, 625 mg BID, and 500 mg BID). OR **Cohort B** – Progression on the first single agent EGFR directed therapy received and also had no more than one previous line of chemotherapy (Dose levels of 750 mg BID, 625 mg BID, and 500 mg BID). OR **Cohort C** – Signed consent for the study, and fulfils eligibility, but with discordance between local (T790M positive) and central (T790M negative) T790M results, or had no central test result due to inadequacy of the tissue specimen and known to be T790M positive by local test (Dose level of 625 mg BID).
Planned Number of Patients	Total number of patients – up to approximately 715 (Phase 1 N≈110; Phase 2 N≈605)

<table>
<tr><td></td><td>

Phase 1: CO-1686 free base (completed) - 57 patients
CO-1686 HBr - approximately 53 patients
Phase 2: Cohort A: Approximately 40 patients for dose level 750 mg BID, up to approximately 275 patients for combined dose levels of 500 mg BID and 625 mg BID
Cohort B: Approximately 40 patients for dose level 750 mg BID, up to approximately 150 patients for combined dose levels of 500 mg BID and 625 mg BID
Cohort C: Up to approximately 100 patients at 625 mg BID.

</td></tr>
<tr><td>Planned Number of Sites</td><td>Phase 1: Approximately 8 investigative sites
Phase 2: Approximately 50 investigative sites in the United States, European Union and Australia</td></tr>
<tr><td>PART 1
Study Objectives and Endpoints for Phase 1</td><td>Primary, secondary and exploratory objectives and endpoints are shown in the following table.
<table>
<tr><th colspan="2">Phase 1</th></tr>
<tr><th>Primary Objectives</th><th>Primary Endpoints</th></tr>
<tr><td>To evaluate the toxicity profile of escalating doses of CO-1686 and to determine the MTD and RP2D</td><td>The incidence of Grade 3 or 4 adverse events (AEs) and clinical laboratory abnormalities defined as dose-limiting toxicities (DLTs)</td></tr>
<tr><td>To characterize the PK profile of CO-1686</td><td>PK parameters including area under the curve from time zero to time t (AUC_{0-t}), AUC from time zero to infinity ($AUC_{0-\infty}$), maximum concentration (C_{max}), time to maximum concentration (T_{max}), elimination half-life ($T_{1/2}$), elimination rate constant (k_{el}), volume of distribution at steady state after nonintravenous administration (V_{ss}/F), and total plasma clearance (Cl/F) for CO-1686</td></tr>
<tr><th>Secondary Objective</th><th>Secondary Endpoints</th></tr>
<tr><td>To characterize the PK profile of CO-1686 after a high-fat breakfast vs in the fasted state</td><td>PK parameters C_{max} and AUC for CO-1686 (fasted and fed)</td></tr>
<tr><td>To evaluate the effects of CO-1686 on the QT/QTc interval</td><td>Change from baseline in QT/QTc interval</td></tr>
<tr><td>To evaluate tumor response (overall response rate [ORR] + duration of response) of CO-1686</td><td>ORR and duration of response per Response Criteria in Solid Tumors (RECIST) Version 1.1</td></tr>
<tr><th>Exploratory Objectives</th><th>Exploratory Endpoints</th></tr>
<tr><td>To characterize lung-cancer and treatment-related symptoms in patients at baseline and in response to CO-1686 using the Dermatology Life Quality Index, the EORTC QLQ - LC13, and the EORTC QLQ-C30.</td><td>Change from baseline in patient-reported outcomes</td></tr>
<tr><td>To explore the concordance of T790M detected in tumor versus that detected in blood.</td><td>Concordance of the presence of T790M mutation in blood and tumor tissue samples</td></tr>
<tr><td>To determine if T790M is detectable in urine (optional sampling).</td><td>Detection of T790M in urine samples</td></tr>
</table>
</td></tr>
</table>

PART 2

Study Objectives and Endpoints for Phase 2 - Expansion Cohorts in T790M Positive Patients

Primary, secondary and exploratory objectives and endpoints are shown in the following table.

Phase 2	
Primary Objectives	**Primary Endpoints**
To evaluate tumor response (ORR + duration of response) to CO-1686 in patients with a T790M mutation	ORR and duration of response per RECIST Version 1.1 by investigator assessment
Secondary Objectives	**Secondary Endpoints**
To evaluate objective response rate (ORR), duration of response, and progression-free survival [PFS] in patients treated with CO-1686	ORR, duration of response and PFS per RECIST Version 1.1 as determined by independent radiology review (IRR)
To evaluate the toxicity and tolerability of CO-1686	The incidence of AEs, clinical laboratory abnormalities, and ECG abnormalities
To evaluate overall survival (OS), disease control rate (DCR), and progression-free survival [PFS] in patients treated with CO-1686	OS, DCR and PFS per RECIST Version 1.1 as determined by investigator assessment
To determine pharmacokinetics (PK) of CO-1686 using population PK (POPPK) methods and explore correlations between PK, exposure, response, and/or safety findings	Plasma PK parameters for CO-1686 at Cycle 1 Day 1 and Cycle 1 Day 15 for a subset of patients; CO-1686 metabolite profile in the Day 15 plasma samples for a subset of patients; Plasma PK parameters for CO-1686 based on sparse sampling of all patients
To characterize lung-cancer and treatment-related symptoms in patients at baseline and in response to CO-1686 using the Dermatology Life Quality Index, the EORTC QLQ - LC13, and the EORTC QLQ-C30.	Change from baseline in patient-reported outcomes
To evaluate the effects of CO-1686 on the QT/QTc interval	Change from baseline in QT/QTc interval
Exploratory Objectives	**Exploratory Endpoints**
To evaluate clinical benefit of continued CO-1686 treatment following disease progression	Time-to-treatment failure
To explore the concordance of T790M detected in tumor versus that detected in blood	Concordance of the presence of T790M mutation in blood and tumor tissue samples

Study Design	This is a two-part, open-label, safety, PK, and efficacy study of oral CO-1686 administered daily in previously treated NSCLC patients who have documented evidence of an activating mutation in the EGFR gene and have failed treatment with an EGFR inhibitor such as erlotinib, gefitinib or afatinib. **Part 1 - Phase 1** The dose escalation phase of Part 1 was completed in January 2014. Eligible patients provided tumor tissue for T790M evaluation by the sponsor's central laboratory but enrolment to Phase 1 was irrespective of T790M status. Each patient was treated with oral CO-1686 daily for a 21-day period and underwent assessments for safety (DLTs, AEs, vital signs, clinical laboratory tests, ECOG performance status, ECG and physical examinations) and PK according to the schedule of assessments. All dose escalation steps were agreed upon between the investigators and the sponsor. The safety monitoring window was 21 days. As of 30 January 2014, 103 patients with advanced NSCLC have received at least one dose of CO-1686. In the initial stage of the study, 57 patients were treated with CO-1686 administered as free base capsules at doses ranging from 150 mg up to 1800 mg daily. Subsequently, CO-1686 hydrobromide (HBr) tablets were introduced into the study and 46 patients were treated with CO-1686 HBr at 500 mg BID, 625 mg BID, 750 mg BID and 1000 mg BID in the dose escalation phase of the study. Dose escalation evaluation was completed in January 2014 and all doses tested had less than 33% incidence of dose limiting toxicities in Cycle 1). A MTD was not identified during Cycle 1 (Safety and PK Assessment Period). In Phase 1, intrapatient dose escalation was permitted by the sponsor if the maximum drug-related toxicity experienced by the patient was ≤Grade 2 and provided that the dose level to which the patient escalate had already been cleared at the time of the proposed dose increase. Existing patients being treated with CO-1686 free base were transitioned to CO-1686 HBr 500 mg BID once safety evaluation of this dose level was completed. When a patient was transitioned to CO-1686 HBr, the new formulation was to be initiated at Day 1of the cycle and, preferably, a full 24-hour PK profile on both Days 1 and 15 was to be repeated. At a minimum, however, the pre-dose PK blood samples were to be collected on Day 1 of each treatment cycle of CO-1686 HBr. Investigators could transition patients to a lower dose of CO-1686 HBr based on their clinical judgment. All Phase 1 patients on freebase were transitioned to CO-1686 HBr by November 2013. <u>RP2D Selection</u> The RP2D for evaluation in Phase 2 was to be selected based on overall safety and tolerability, PK, and estimates of efficacious exposures extrapolated from nonclinical data and Phase 1 of the study. The RP2D could or might not be the same as the MTD identified in Phase 1. If an MTD was not identified in the dose range expected, a dose that met the tolerability and PK criteria could be selected as the RP2D and dose escalation could continue concurrently to fully explore the exposure and dose relationship. If it is determined that a higher or lower dose in one of the further escalation cohorts is considered likely to be superior to the originally selected RP2D, patients in the Phase 2 cohort may be escalated to the new RP2D dose if they meet the intrapatient dose escalation criteria.

	Food-effect PK Evaluation The effect of food on oral CO-1686 PK was assessed in a subset of patients. PK Evaluation of Once-daily Dosing Versus Twice-daily or Three-times-daily Dosing was started with once-daily (QD) dosing, and subsequently the effect of twice-daily (BID) and three-times-daily (TID) dosing on oral CO-1686 PK was assessed in a subset of patients. Effect on QTc In Phase 1, Serial ECG monitoring is performed: at baseline, on Cycle 1 Day 1 and Cycle 1 Day 15 (prior to dosing and at multiple time points as described in Table 13 following dosing with CO-1686) and on Day 1 of all subsequent cycles [prior to dosing and at the estimated T_{max} (2 hours) postdose], at the End of Treatment, and as clinically indicated in order to assess the effect of oral CO-1686 on the QTc interval. All ECGs are performed on equipment provided by the sponsor (or designee) and reviewed by site personnel and a core/central laboratory. Treatment-extension Period Upon completion of Cycle 1 (Safety and PK Assessment Period), Phase 1 patients could participate in an optional Treatment-extension Period, with ongoing safety and activity monitoring, which begins on Day 1 of Cycle 2. Oral CO-1686 is administered daily during this period (21-day cycles). Protocol-specified treatment will continue until there is progression by RECIST Version 1.1, clinical tumor progression or unacceptable toxicity as assessed by the investigator. 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. In general, eligible patients may include those with asymptomatic systemic progression or locally symptomatic progression, such as brain metastases amenable to local treatment, with concomitant asymptomatic systemic progression or continued systemic disease control. Patients will undergo serial assessments for anti-tumor efficacy, drug safety, and patient reported outcomes. Serial blood sampling for longitudinal quantitative assessment of ctDNA will be conducted. Following disease progression on CO-1686, patients can consent to participate in an optional additional biopsy before subsequent-line therapy is initiated. As of 6 March 2014, 49 patients are continuing to receive treatment in Phase 1 of this study. **Part 2 - Phase 2** The additional dose levels added to cohorts A and B and increased patient numbers introduced in Amendment 6 allows a comprehensive assessment of dose and response across doses that have exhibited clinical activity to date. The addition of Cohort C will provide an estimate of activity in patients with a positive T790M local test, but discordant central test results or missing central test results due to inadequacy of the tissue specimen by central test, and will allow CO-1686 treatment based on a local T790M positive result only.

	The Phase 2 portion of the study will consist of a screening phase to establish study eligibility and document baseline measurements, an open-label treatment phase, in which patients will receive CO-1686 to ascertain safety and efficacy until protocol-defined disease progression. Each 21-day period of treatment will represent one cycle, with dosing initiated on Cycle 1 Day 1. Eligible patients are those who are confirmed by the sponsor's central laboratory (Cohorts A and B) or by local assessment (Cohort C) to have the T790M mutation in FFPE tumor tissue. The assessments for patients in each Phase 2 cohorts will be identical. Enrollment into Part 2 was initiated in January 2014 under Amendment 4 when a RP2D of 750 mg BID was selected based on early efficacy Phase 1 data, and two expansion cohorts (Cohorts A and B) are enrolling at this dose. As the Phase 1 efficacy data matured, the recommended dose was adjusted to 625 mg BID, and under Amendment 6, patients will no longer enroll in the 750 mg BID dose level for Cohorts A and B, but will be assigned by the sponsor to receive either 625 mg BID or 500 mg BID. Patients who are already receiving 750 mg BID will continue at this dose. Separately within each new dose level in Cohorts A and B combined (500 mg BID and 625 mg BID), the objective response rate will be evaluated in the first 12 patients. Within Cohort C, the objective response rate will be evaluated separately for patients from the 2 patient populations represented by Cohorts A and B. If 0 responses are observed in the first 12 patients within each dose level (combined Cohorts A and B) or patient population (Cohort C) are observed then the respective level or population may be discontinued due to a lack of efficacy. If zero PR or CR responses are observed in 12 patients then there is a high probability that the true objective response rate is less than 20%. In addition to the futility analyses within each cohort, formal safety data reviews will occur following the enrollment of every 50 patients and approximately every 6 months once enrollment is completed and as long as patients remain on treatment. The review committee will include external experts and sponsor personnel. The external experts will include, but not be limited to, the coordinating PIs of the study. The sponsor's reviewers will include the Medical Monitor, Chief Medical Officer, and Biostatistician. The protocol will be amended as appropriate to incorporate additional patient safety monitoring if new safety signals are noted at any review. If a dose level is closed for further evaluation because of lack of activity, ongoing patients in that dose level may be allowed to dose escalate to a higher dose level if they meet the intra-patient dose escalation criteria. For all Phase 2 patients, protocol-specified treatment will continue until there is progression by RECIST Version 1.1, clinical tumor progression or unacceptable toxicity as assessed by the investigator. 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. In general, eligible patients may include those with asymptomatic systemic progression or locally symptomatic progression, such as brain metastases amenable to local treatment, with concomitant asymptomatic systemic progression or continued systemic disease control. Patients will undergo serial assessments for anti-tumor

	efficacy, drug safety, and patient reported outcomes. Serial blood sampling for longitudinal quantitative assessment of ctDNA will be conducted. Local laboratories will be used for hematology and chemistry assessment. A central laboratory will be used for ECG interpretation. Tumor assessments will be performed by the investigative site and scans will be evaluated locally for patient treatment decisions; however, copies of tumor scans will be collected centrally to facilitate independent evaluation for ORR, duration of response, PFS and other assessments if deemed necessary by the sponsor. Following disease progression on CO-1686, patients can consent to participate in an optional additional biopsy before subsequent-line therapy is initiated. **Extension Phase (Phase 1 and Phase 2 Patients)** 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 are 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 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 the study at the discretion of the Principal Investigator in the Extension Phase. The purpose of this protocol amendment (Amendment 8) is to add a new Extension Phase to allow patients to continue on the 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 has been provided in Appendix D that will be applicable to both ongoing Phase 1 and Phase 2 patients. This schedule will replace all schedules of assessments in Section 9.1. In addition, Amendment 8 (Appendix D) 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 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 important that a full exploration of alternative treatment options between patients and their treating physicians takes place. Finally, 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 presented in this protocol. <u>CO-1686 PK and Metabolite Profiling</u> A subset of 10 patients at dose levels of 500 mg BID and 625 mg BID, at a minimum, in Phase 2 will have a detailed PK profile taken over Cycle 1 Day 1 and Cycle 1 Day 15. In addition, at the 625 mg dose level, at a minimum, three of the subset of 10 patients will have additional blood samples collected on Day 1 (predose sample only) and Day 15 (postdose) of Cycle 1 for assessment of plasma metabolites of CO-1686. All patients in Phase 2 will have PK samples collected on Cycle 1 Day 15, and on Day 1 of every subsequent cycle beginning with Cycle 2 up to and including Cycle 9 (Section 9.8.3.2). <u>Effect on QTc</u>

	In the subset of patients for whom a detailed PK profile will be collected in Phase 2, ECG monitoring will be performed: at baseline, on Cycle 1 Day 1 and Cycle 1 Day 15 (prior to dosing and at the multiple time points as described in Table 13 following dosing with CO-1686), and on Day 1 of all subsequent cycles [prior to dosing and at the estimated T_{max} (2 hours) postdose], at the End of Treatment, and as clinically indicated in order to assess the effect of oral CO-1686 on the QTc interval. In all other Phase 2 patients, serial ECG monitoring will be performed: at baseline, on Cycle 1 Day 1, Cycle 1 Day 15 and on Day 1 of all subsequent cycles [prior to dosing and at the estimated T_{max} (2 hours) postdose at these visits], at the End of Treatment, and as clinically indicated. All ECGs will be performed on equipment provided by the sponsor (or designee) and reviewed by site personnel and a core/central laboratory. <u>Phase 1 and Phase 2: End of Treatment and Safety Follow-up</u> All patients should return to the clinic for End of Treatment assessments 28 (±7) days after the last dose of CO-1686 has been administered. All Phase 2 patients will be followed at approximately two monthly intervals to monitor survival status and subsequent NCSLC therapy until death or sponsor decision, whichever comes first. After discontinuation of protocol-specified treatment, subsequent anticancer therapy use will be recorded.
Dose-limiting Toxicities	DLTs are defined as any of the following events that occur during Cycle 1 (Safety and PK Assessment Period) in patients enrolled into a DLT evaluable cohort in Phase 1, and are assessed by the investigator as probably, possibly or definitively related to CO-1686. Where applicable, events will be classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0.[10] Dose limiting toxicities include: • Grade 3 or 4 skin eruption, nausea, vomiting, diarrhea or hyperglycemia despite the use of adequate/maximal medical intervention and/or prophylaxis • Any Grade 4 skin rash/eruption with extensive superinfection requiring IV antibiotics and with life-threatening consequences (e.g., rash acneiform, papulopustular rash, Stevens-Johnson Syndrome) • Any nonhematological CTCAE Grade 3 or greater AE (except alopecia or nausea, vomiting, diarrhea or hyperglycemia if well-controlled by systemic medication) • Absolute neutrophil count (ANC) $< 0.5 \times 10^9$/L > 5 days duration or febrile neutropenia (i.e., fever > 38.3°C with ANC $< 1.0 \times 10^9$/L) • Platelets $< 25 \times 10^9$/L or platelets $< 50 \times 10^9$/L with bleeding requiring a platelet transfusion • Grade 4 anemia (life-threatening consequences, urgent intervention indicated). Delayed recovery from toxicity related to CO-1686 treatment that delays scheduled retreatment for > 14 days

Study Population	Inclusion Criteria All patients enrolling into either Phase 1 or Phase 2 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 one or more EGFR mutations excluding exon 20 insertion 3. Have undergone a biopsy of either primary or metastatic tumor tissue within 60 days of dosing with study drug and have tissue available to send to the sponsor's lab or are able to undergo a biopsy during screening • No change (except for washout or dose adjustment if required to manage adverse effects) in antitumor therapy regimen is allowed between the biopsy and CO-1686 initiation. 4. Life expectancy of at least 3 months 5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 6. Age ≥18 years 7. Adequate hematological and biological function, confirmed by the following screening laboratory values: Bone Marrow Function 1. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L 2. Platelets >100.0 × 10^9/L 3. Hemoglobin ≥9 g/dL (or 5.6 mmol/L) Hepatic Function 4. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3 × upper limit of normal (ULN); if liver metastases, ≤5 × ULN 5. Bilirubin ≤2 × ULN* Renal Function 6. Serum creatinine ≤1.5 × ULN Electrolytes 1. Potassium and magnesium within normal range. Patients may receive supplements to meet this requirement 2. Written consent on an Institutional Review Board/Independent Ethics Committee-approved Informed Consent Form (ICF) prior to any study-specific evaluation *Patients with documented Gilbert's syndrome and conjugated bilirubin within the normal range may be allowed into the study. In this event it will be documented that the patient was eligible based on conjugated bilirubin levels

Patients enrolling into **Phase 1** must also meet the following inclusion criteria:

- Prior treatment with EGFR-directed therapy (e.g. erlotinib, gefitinib, neratinib, afatinib, or dacomitinib [PF299804]). Prior chemotherapy, including intervening chemotherapy, is allowed.
  - The washout period for an EGFR TKI is a minimum of 3 days
  - The washout period for chemotherapy is a minimum of 14 days
  - Any toxicity related to prior treatment must have resolved to Grade 1 or less

Be willing and able to eat a high-fat breakfast on Day 1 of the study (*only applicable to food-effect cohort).*

Patients enrolling into **Phase 2 Cohort A** must also meet the following inclusion criteria:

- Disease progression confirmed by radiologic assessment while on treatment with EGFR- TKI (e.g. erlotinib, gefitinib, neratinib, afatinib, or dacomitinib). Prior chemotherapy, including intervening chemotherapy before planned initiation of CO-1686, is allowed.
  - The washout period for an EGFR TKI is a minimum of 3 days before planned Cycle 1 Day 1
  - The washout period for chemotherapy is a minimum of 14 days before planned Cycle 1 Day 1
  - Any toxicity related to prior treatment must have resolved to Grade 1 or less by Cycle 1 Day 1
- Documented evidence of T790M mutation in EGFR determined by PCR-based testing of the tumor tissue using the sponsor' central lab following disease progression on the most recent EGFR TKI therapy.
- Measurable disease according to RECIST Version 1.1.
- Do not qualify for enrolment to Phase 2 Cohort B*

*Patients meeting eligibility criteria for Cohort B must be enrolled into this cohort rather than Cohort A.

Patients enrolling into **Phase 2 Cohort B** must also meet the following inclusion criteria:

- Disease progression confirmed by radiologic assessment while on treatment with the <u>first single agent EGFR TKI</u> (e.g. erlotinib, gefitinib, afatinib, or dacomitinib)
  - EGFR TKI treatment discontinued ≤ 30 days prior to planned initiation of CO-1686
  - The washout period for an EGFR TKI is a minimum of 3 days before planned Cycle 1 Day 1
  - 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 by Cycle 1 Day 1
- Documented evidence of T790M mutation in EGFR as determined by PCR-based testing of tumor tissue using the sponsor's central lab following disease progression on the first single agent EGFR TKI.
- Measureable disease according to RECIST Version 1.1

Patients enrolling into **Phase 2 Cohort C** must also meet the following inclusion criteria:

- Must meet all inclusion criteria of other Phase 2 Cohorts A or B except for documented evidence of T790M mutation using the sponsor's ***<u>central lab</u>***
- Only patients with evidence of a positive T790M mutation result from a local lab but with an insufficient specimen for central lab analysis (judged by the central lab analysis) or a negative central T790M mutation result from the same biopsy specimen collected within 60 days of treatment with CO-1686

<u>Exclusion Criteria</u>

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. Patients with Leptomeningeal carcinomatosis are excluded. Other CNS metastases are only permitted if treated, asymptomatic, and stable (not requiring steroids for at least 4 weeks prior to start of study treatment). 5. Treatment with prohibited medications [e.g., concurrent anticancer therapy including other chemotherapy, radiation therapy, or 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 7. Prior treatment with CO-1686 or other drugs that target T790M positive, mutant EGFR with sparing of wild type EGFR, e.g. AZD9291, HM61713, TAS-121 8. Any of the following cardiac abnormalities or history: a. Clinically significant abnormal 12-lead ECG, QT interval corrected using Fridericia's method (QT_CF) > 450 msec b. Inability to measure QT interval on ECG c. Personal or family history of long QT syndrome d. Implantable pacemaker or implantable cardioverter defibrillator e. Resting bradycardia < 55 beats/min 9. Non-study 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) 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 (e.g., substance abuse, uncontrolled intercurrent illness including active infection, arterial thrombosis, and symptomatic pulmonary embolism) Any other reason the investigator considers the patient should not participate in the study
Study Treatment	Under Amendment 6 and subsequent amendments, CO-1686 will be administered to patients as oral tablets in a twice daily regimen. Patients will be instructed to take CO-1686 at the specified dose for the dosing level with a meal or within 30 minutes after a meal.
Interim Safety Monitoring and Futility Analyses	Separately within each new dose level in Cohorts A and B (500 mg BID and 625 mg BID), the objective response rate will be evaluated in the first 12 patients. Within Cohort C, the objective response rate will be evaluated separately for patients from the 2 patient populations represented by cohorts A and B. If 0 responses are observed in the first 12 patients within each dose level (Cohorts A and B) or patient population (Cohort C) are observed then the respective level or population may be discontinued due to a lack of efficacy. If zero PR or CR responses are observed in 12 patients then there is a high probability that the true objective response rate is less than 20%. In addition to the futility analyses within each cohort, formal safety data reviews will occur following the enrollment of every 50 patients and approximately every 6 months once enrollment is completed and as long as patients remain on treatment. The review committee will include external experts and sponsor personnel. The external experts will include, but not be limited to, the coordinating PIs of the study. The sponsor's reviewers will include the Medical Monitor, Chief Medical Officer, and Biostatistician. The protocol will be amended as appropriate to

	incorporate additional patient safety monitoring if new safety signals are noted at any review.
Dose-modification Criteria	Dose reduction steps are allowed for each patient in Phase 1 or Phase 2, with the overall number of dose reduction steps at the investigator's discretion. Dose reductions can occur in 125 mg increments BID from the starting dose (e.g. from 625 mg BID to 500 mg BID). For non-serious adverse events, a TID dosing regimen may be used to maintain plasma exposure, whilst reducing the peak plasma concentrations which may drive toxicity (e.g. from 625 mg BID (1250 mg total dose/day) to 375 mg TID (1175 mg total dose/day) or 500 mg BID (1000 mg total dose/day) to 250 mg TID (750 mg total dose/day)]. 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 to the next lower dose BID and, if persistent, can be further reduced (250 mg increment BID less than starting dose) for subsequent doses if the investigator and the sponsor do not believe treatment discontinuation is required. Re-escalation of dose after resolution of adverse events must be discussed and approved by the sponsor. Dose reductions below 250 mg increment BID less than starting dose must be discussed and agreed with the sponsor before they are implemented. ECGs will be measured throughout the study as described in the protocol. If QT_C prolongation of CTCAE Grade 3 is observed, CO-1686 will be held until the event has improved to Grade 1. CO-1686 can then be re-started at a reduced dose after sponsor approval. After two dose reduction evaluations, 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 7.4.3.
Concomitant Medications	Supportive care (e.g., 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 in Section 5.1.4 • 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 • Non-compliance as described in Section 7.7 • A positive pregnancy test at any time during the study
Pharmaco-genetic Assessments	For patients who provide additional consent, genomic DNA will be extracted from a blood sample from each patient in Phase 1 and Phase 2 to detect genetic polymorphisms in CYP isoenzymes in order to explore the correlation between CYP polymorphism and drug exposure.

Biomarker and Exploratory Assessments	Tumor tissue from the primary tumor, or an accessible metastatic lesion, will be obtained within 60 days prior to dosing as described in Section 9.8.4 of the protocol. When sufficient tissue is available from the baseline tumor biopsy, samples may be tested for molecular alterations that may modulate response or resistance to EGFR-targeted therapy. Patients who provide additional consent will undergo an optional tumor biopsy at disease progression. This tissue may be analyzed for molecular alterations that modulate resistance to EGFR-targeted therapy. 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. Analysis may not be performed or only performed on a subset of patients if it becomes clear that the analysis will have limited scientific value (e.g., because of a very low titer of ctDNA in some patients, or if there are not enough serially collected samples from individual patients to allow for adequate biomarker evaluation). Patients who provide additional consent in Phase 1 and Phase 2 will provide urine specimens pre-dose on Day 1 of Cycles 1 to 6 and at the End of Treatment visit to determine whether biomarkers including T790M are detectable in transrenal nucleic acids.
Pharmacokinetic Assessments	Patients enrolled in Phase 1 and a subset of 10 patients at the dose levels of 500 mg BID and 625 mg BID in Phase 2 will have PK sampling during Cycle 1, with collection time points predose and from 15 min through 24 hr postdose on Days 1 and 15. For Phase 1 patients in Cycles 2 and beyond, and for Phase 2 patients not participating in the full PK evaluation, only single trough-level PK samples will be collected during the treatment period. Patients participating in the in the food-effect PK evaluation will have an additional PK sampling on Day -7. PK evaluations will be based on the determination of the following parameters for CO-1686 including (but not limited to): AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, $T_{1/2}$, and k_{el} V_{ss}/F, and Cl/F. A central/core laboratory will be used for the PK assay. A profile of circulating metabolites of CO-1686 at steady state will be evaluated in at least three patients at the RP2D (625 mg BID).
Quality of Life Assessments	Quality of life will be measured using the EORTC QLQ C30 and LC13 and the Dermatology Life Quality Index (DLQI), which will be administered at baseline, every 2 cycles through Cycle 6, and then every 3 cycles thereafter.[11,12]

Efficacy Assessments	Efficacy measures (Phase 1 and Phase 2) will include tumor assessments, consisting of clinical examination and appropriate imaging techniques (preferably computed tomography (CT) scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST Version 1.1); other studies (magnetic resonance imaging [MRI] and X-ray) may be performed if required. Patients with an initial PR or CR at Cycle 7 or beyond will have confirmatory scan performed 4 to 6 weeks 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 6 to 8 weeks. All patients require baseline brain scans and those with brain metastases at baseline will require repeat brain imaging as part of the follow-up tumor assessments. Tumor assessments will be performed at screening; at the end of Cycles 2, 4, and 6 (between Days 14 and 21); every three cycles after Cycle 6 (between Days 14 and 21); and at the End of Treatment visit, if disease progression has not been documented previously.
Safety Assessments	Safety measures will include: • AEs • Hematology, including reticulocyte count, clinical chemistry including fasting glucose and HbA1c, and urinalysis • 12-lead ECGs • Physical examination • Vital signs and body weight • Concomitant medications/procedures • ECOG performance status
Statistical Procedures	**Analysis Populations** • PK-evaluable population: all patients who received CO-1686 and have adequate PK blood draws for determination of the PK profile. Adequacy will be determined on a case-by-case basis and will be assessed prior to analysis of the blood samples. • DLT-evaluable population: all patients enrolled into Phase 1 who received at least 80% of the scheduled doses of CO-1686 and completed Cycle 1 of treatment, or who experienced a DLT in Cycle 1. • Food-effect PK population: all patients who enrolled into a food effect PK evaluation cohort who received CO-1686 on both Day -7 and Day 1, complied with the fed and fasted requirements, and have sufficient PK data for a comparison to be made between the fasted and fed state. • ECG/PK comparison-evaluable population: all patients in Phase 1 and Phase 2 who have received CO-1686 and have had adequate PK and ECG assessments performed for determination of the ECG effects and the relationship between PK and ECG. • Safety population: all patients who have received at least one dose of CO-1686.

	• Tumor-evaluable population: all patients who received at least one dose of CO-1686, have at least one measurable tumor lesion at baseline, and have at least one post-baseline tumor assessment. **Sample Size Justification** Amendment 6 allowed for up to approximately 380 efficacy-evaluable patients to be enrolled into Cohorts A, B and approximately 100 efficacy-evaluable patients in Cohort C for the Phase 2 portion of the study. Amendment 7 increased the total patient number in Cohort A to allow for patients to continue to enroll in Cohort A as long as Cohort B was still open to enrollment, which was estimated to increase the total patient number in this study by approximately 125 patients. **Pharmacokinetic Analyses** PK parameters will be determined using non-compartmental methods.
	Relationship Between PK and QTc The effects of CO-1686 on the QT/QTc interval of the electrocardiogram (ECG) will be measured by the change in baseline-adjusted QTcF (ΔQTcF) from Day 1 (at selected time points outlined in Table 13), Day 15 (at selected time points outlined in Table 13), on Day 1 of all subsequent cycles (prior to dosing and at the estimated T_{max} (2 hours) postdose), and at End of Treatment for all Phase 1 and a subset of Phase 2 patients participating in full PK profiling. Other QTc analyses will repeat the analysis using other heart rate correction methods. **Efficacy Analysis** The overall response rate will be summarized with frequencies and percentages. The duration of response for complete response (CR), partial response (PR), overall survival (OS) and duration of stable disease will be summarized with descriptive statistics (N, mean, standard deviation, median, minimum, and maximum) as well as categorically. Disease control rate (DCR) is defined as the percentage of patients who have achieved CR, PR, and SD for a minimum of 12 weeks. Kaplan-Meier methodology will be used to summarize PFS and OS. **Safety Analyses** Data from all patients who receive one or more doses of CO-1686 will be included in the safety analyses. AEs, clinical laboratory information, vital signs, ECOG performance status, body weight, and concomitant medications/procedures will be tabulated and summarized. **Population PK** Blood sampling for population PK analyses will be conducted in all patients treated with CO-1686. A specific population PK data analysis plan will be developed and will outline the detailed approach to data handling, model development and diagnostics, individual model parameter estimation, exploration of covariate effects, and final model evaluation techniques.

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AAG	alpha-1 acid glycoprotein
AE	adverse event
ALK	anaplastic lymphoma kinase
ALT	alanine transaminase
ANC	absolute neutrophil count
ANOVA	analysis of variance
AST	aspartate transaminase
AUC	area under the curve
AUC_{0-24}	area under the curve from time zero to 24 hours
$AUC_{0-\infty}$	area under the curve from time zero to infinity
AUC_{0-t}	area under the curve from time zero to time t
BID	twice daily
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence interval
Cl/F	total plasma clearance after oral administration
C_{min}	minimum concentration
C_{max}	maximum concentration
CR	complete response
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events (Version 4.0)
CYP	cytochrome P450
DLQI	Dermatology Life Quality Index
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EORTC QLQ LC13	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, Lung Cancer 13
EOT	End of Treatment
EU	European Union

EURTAC	European Tarceva versus Chemotherapy Study
FACT-L	Functional Assessment of Cancer Therapy-Lung questionnaire
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FOB	functional observation battery
GCP	Good Clinical Practice
GI_{50}	concentration required to reduce growth of treated cells to 50% of untreated cells
GLP	Good Laboratory Practice
GRAS	generally regarded as safe
hERG	human ether-a-go-go-related gene
HIPAA	Health Information Portability and Accountability Act
HNSTD	highest non-severely toxic dose
HPLC-UV-MS/MS	high-performance liquid chromatography coupled with ultraviolet spectrophotometric and tandem mass spectrometric detection
HPMC	hydroxyprophyl methylcellulose
HR	hazard ratio
IC_{50}	concentration at 50% maximal inhibition
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
ILD	interstitial lung disease
iPASS	Iressa Pan-Asian Study
IRB	Institutional Review Board
IV	Intravenous
K_d	dissociation constant
k_{el}	elimination rate constant
MAPK	mitogen-activated protein kinase
MRI	magnetic resonance imaging
MRSD	maximum recommended starting dose
MTD	maximum tolerated dose
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
ORR	objective response rate or overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PE	Polyethylene

PEG	polyethylene glycol
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PO	Oral
PPI	proton pump inhibitor
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
QD	once daily
QTcF	QT interval corrected using Fridericia's method
RECIST	Response Evaluation Criteria in Solid Tumors, Version 1.1
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis software
SCID	severe combined immunodeficiency
STD_{10}	severely toxic dose in 10% of animals
SUSAR	suspected unexpected serious adverse reaction
$T_{1/2}$	elimination half-life
T790M	EGFR mutation in exon 20, gatekeeper mutation
TGI	tumor growth inhibition
TID	three times daily
TKI	tyrosine kinase inhibitor
T_{max}	time to maximum concentration
TNM	tumor/node/metastasis
TOI	Trial Outcome Index
TPGS	tocopherol polyethylene glycol succinate
ULN	upper limit of normal
US	United States
V_{ss}/F	volume of distribution at steady state after non-IVadministration
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 are 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 the study at the discretion of the Principal Investigator in an extension phase. No further patients will be enrolled in this study.

3.1.1 *Extension Phase*

The purpose of this protocol amendment (Amendment 8) is to add a new Extension Phase to allow patients to continue on study but to avoid unnecessary collection of data that will no longer be analyzed or required for regulatory purposes, whilst maintaining an appropriate level of safety monitoring. A new schedule of assessments for the Extension Phase as well as a complete description of procedures is provided in Appendix D. This schedule replaces all schedules of assessments in Section 9.1 and should be followed for all patients.

In addition, Amendment 8 (Appendix D) 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 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.

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 approximately 1.35 million new cases annually, and non-small cell lung cancer (NSCLC) accounting for almost 85% of all lung cancers.[1] Additionally, lung cancer continues to be the most common cause of cancer-related deaths worldwide[13] with a 5-year survival rate of less than 10%[14] in patients with advanced disease.

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 two single-arm studies of crizotinib in previously treated ALK-positive patients, the tumor response rates were 50% and 61% and the duration of responses were 42 and 48 weeks, respectively.[15] These response rates and the duration of response are significantly higher that what would be expected with chemotherapy in this patient population.[16]

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.[3] Two recent Phase 3 trials comparing tyrosine kinase inhibitors (TKIs) versus chemotherapy have established TKIs as the gold standard for treating EGFR-mutation-positive NCSLC. In the Iressa Pan-Asia Study (iPASS) trial, treatment with gefitinib was compared to treatment with carboplatin/paclitaxel in previously untreated NSCLC patients. In EGFR-mutation-positive patients, the response rate was significantly higher with gefitinib treatment (71.2%) than with chemotherapy (47.3%).[2] Furthermore, EGFR-mutation-positive patients experienced a significantly longer progression free survival (PFS) of 9.5 months compared to 6.3 months for those on chemotherapy.[17] Quality of life was also evaluated in this study; more patients treated with gefitinib versus chemotherapy had clinically meaningful improvement in quality of life, as assessed by the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire and Trial Outcome Index (TOI).2 Although survival was an endpoint of the study, the analysis of overall survival was complicated by the fact that EGFR-mutation-positive patients assigned to the chemotherapy arm crossed over to gefitinib upon progression.[17] A second Phase 3 randomized trial, the European Tarceva (erlotinib) versus chemotherapy (EURTAC) study, compared treatment with erlotinib to chemotherapy in previously untreated patients with EGFR-mutation-positive NSCLC. Data from this study show that patients demonstrate a response rate of 58% in the erlotinib arm compared to 15% in the chemotherapy arm ($p < 0.0001$). Furthermore, PFS was 9.7 months in the erlotinib arm versus 5.2 months in the chemotherapy arm [hazard ratio (HR) = 0.37; $p < 0.0001$].[18] At an interim analysis, overall survival was 22.9 months in the erlotinib arm and 18.8 months in the chemotherapy arm (HR = 0.80; $p = 0.42$). Again, crossover 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 to chemotherapy.

While the toxicity profile is also improved with first-generation TKIs compared to chemotherapy, significant toxicities do occur. Toxicity 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.[4,5,6]

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.[19] 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 50% of patients) was found to a second

site EGFR mutation in exon 20 called T790M (the "gatekeeper" mutation), which prevents drug from binding to the receptor.[3,7,8,19] 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* gene amplification). Still others showed mutations in the PIK3CA gene. Interestingly, a few patients had tumors that transitioned to a small cell lung cancer, or to a more aggressive mesenchymal cell morphology.[19]

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.[20] 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 failed 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% CI, 1.6–2.6 years).[21] These patients are usually offered chemotherapy, which is known to cause increased toxicities compared to 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 may 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 (e.g., skin rash and diarrhea).

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), is developing CO-1686 as a therapeutic agent to be administered orally to patients with mutant EGFR NSCLC. CO-1686 inhibits the EGFR gatekeeper mutation (T790M) which is associated with clinical resistance to Tarceva (erlotinib) and Iressa (gefitinib) as well as the common EGFR activating mutations (L858R, del19) and has minimal inhibitory activity towards the $EGFR^{WT}$ 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.

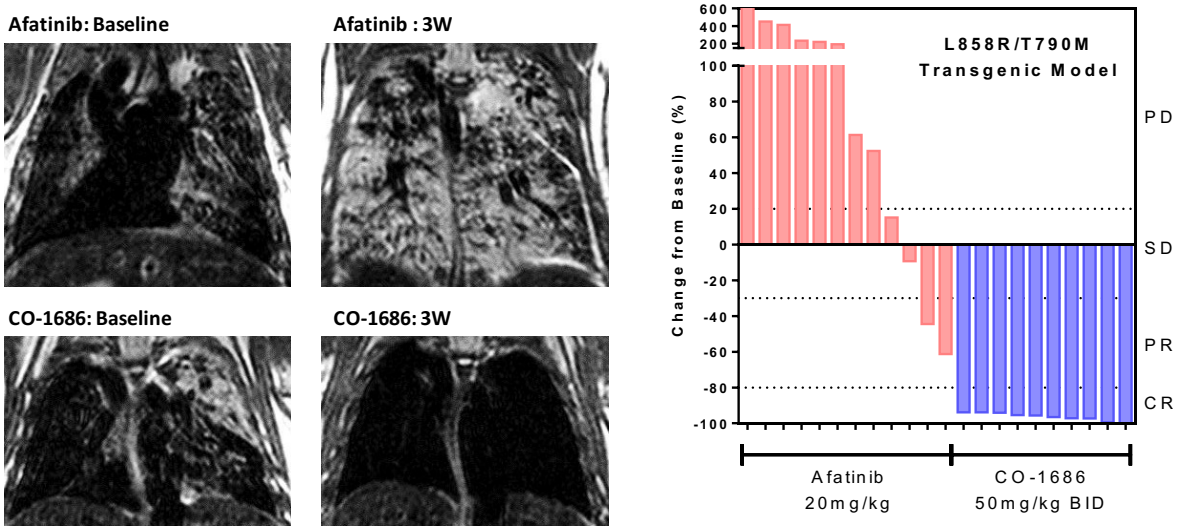
Pharmacology

CO-1686 exhibits nonclinical anti-tumor 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.[22] In addition, the efficacy of CO-1686 was examined in an $EGFR^{L858R/T790M}$ transgenic model and compared with that of afatinib. Complete responses were observed in all mice treated with CO-1686, with very limited activity in the afatinib group (Figure 1).

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



Metabolism

In liver microsomes, CO-1686 was slowly metabolized, with CYP2C8 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 oral CO-1686 and requiring concomitant medication with warfarin (Coumadin), nonsteroidal anti-inflammatory drugs (NSAIDs), or clopidogrel, as CO-1686 moderately inhibited CYP2C8, CYP2C9 and CYP2C19 activities *in vitro.* 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 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. The redness of gingiva or lips noted, had no microscopic correlation at total exposures of AUC of up to 23,100 ng.h/mL.

No evidence of elevated serum glucose levels were observed in the rat and dog studies. There were no CO-1686-related cardiac safety or neurobehavioral findings from the 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 preclinical program.

3.4 Clinical Experience with CO-1686

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

3.4.1 *Safety*

Study CO-1686-008

CO-1686-008 is a two-part, open-label, safety, PK, and preliminary efficacy study of CO-1686 in patients with advanced NSCLC. As of 30 January 2014, 103 patients with advanced NSCLC have received at least one dose of CO-1686. In the initial stage of the study, 57 patients were treated with CO-1686 administered as free base capsules at doses ranging from 150 mg up to 1800 mg daily. Subsequently, CO-1686 hydrobromide tablets were introduced into the study to be used in the later dose escalation cohorts. Forty-six patients have been treated with CO-1686 administered as hydrobromide tablets at doses of 500 mg BID (N = 15), 625 mg (N = 16), 750 mg BID (N = 9) and 1000 mg BID (N = 6). At the time of this summary, preliminary safety data are available in the clinical database for 93 patients.

Dose-limiting Toxicities: The dose limiting toxicity (DLT) evaluable population includes all patients who have completed Cycle 1, and who were enrolled while the dose escalation part of the study was ongoing. 7 patients have experienced DLTs across 6 dose levels (Table 1). A DLT rate > 33% was not reached at any dose. The most frequently reported DLT was hyperglycemia/glucose tolerance impaired which occurred at a similar frequency (11% to 25%) across all CO-1686 HBr dose levels (500 mg BID, 625 mg BID, 750 mg BID and 1000 mg BID). Hyperglycemia can be effectively managed with the addition of oral anti-hyperglycemic therapy and/or dose reductions. Guidance for the management of hyperglycemia associated with CO-1686 treatment is provided in Section 7.4.3.

Table 1: Cycle 1 DLTs Reported for Patients by Dose Level

Starting Dose and Formulation	N evaluated	N with DLT	Description of Event
150 mg QD Free base	6	1 (17%)	One patient experienced hypoglycaemia (Grade 4) on Day 15, a PK fasting day. The patient was known to have diabetes, and the overnight fast and concurrent use of the oral hypoglycemic agents glipizide and metformin significantly contributed to the event. The patient discontinued from the study.
200 mg - 1200 mg daily, Free base, N =18, No DLTs			
900 mg BID Free base	6	1 (17%)	One patient experienced an acute illness on day 3 with dehydration (Grade 3), aspartate aminotransferase (AST) elevation (Grade 3), anorexia (Grade 3), and diarrhea and abdominal cramps. The patient recovered 2-4 days later.
500 mg BID HBr	6	1 (17%)	One patient experienced hyperglycemia (Grade 3) and was diagnosed with pancreatitis (Grade 2), 3 weeks after initiating CO-1686. The patient recovered and continued with dose reduction and anti-hyperglycemic medication.
625 mg BID HBr	8	2 (25%)	One patients experienced fatigue (Grade 3) approximately a week into treatment. The patient recovered 6 days later. One patients experienced hyperglycemia (Grade 3) approximately a week into treatment. The patient recovered and continued with dose reduction and anti-hyperglycemic medication.
750 mg BID HBr	9	1(11%)	One patient experienced hyperglycemia (Grade 3) and electrocardiogram QT prolongation (Grade 3) and T wave inversion (Grade 3). The patient recovered, but withdrew consent before drug was restarted.
1000 mg BID HBr	6	1 (17%)	One patient experienced hyperglycemia (Grade 3) and an increase in INR (Grade 3). The patient recovered and continued with dose reduction and anti-hyperglycemic medication.

SAEs: A total of 28 patients experienced at least 1 SAE and 10 patients have reported an SAE assessed as related to study drug. Treatment related SAEs are summarized in Table 2.

There were six deaths while on study or within 28 days after last dose. All deaths were due to progression of NSCLC and assessed as not related to study drug.

Table 2: Treatment-related SAEs Reported in Any Patient

Daily Dose	< 1800 mg	1800 mg FB	1000 mg	1250 mg	1500 mg	2000 mg	Overall
Formulation	Free base	Free base	HBr	HBr	HBr	HBr	
Frequency	Various [a]	900 mg BID	500 mg BID	625 mg BID	750 mg BID	1000 mg BID	
N	38	19	9	12	9	6	93
Overall	4 (11%)	1 (5%)	1 (11%)	1 (8%)	2 (22%)	1 (17%)	10 (11%)
Cardiac Disorders							
Pericarditis	1 (3%)	0	0	0	0	0	1 (1%)
Gastrointestinal Disorders							
Diarrhea	1 (3%)	1 (5%)	0	0	0	0	2 (2%)
Nausea	1 (3%)	0	0	0	0	0	1 (1%)
Pancreatitis	0	0	1 (11%)	0	0	0	1 (1%)
Vomiting	2 (5%)	0	0	0	0	0	2 (2%)
Investigations							
Electrocardiogram QT prolonged	0	0	0	0	1 (11%)	0	1 (1%)
Electrocardiogram T wave inversion	0	0	0	0	1 (11%)	0	1 (1%)
Transaminases increased	0	1 (5.3%)	0	0	0	0	1 (1%)
Metabolism and Nutrition Disorders							
Decreased Appetite	0	1 (5%)	0	0	0	0	1 (1%)
Hyperglycemia	1 (3%)	0	1 (11%)	1 (8%)	2 (22%)	1 (17%)	6 (7%)
Hypoglycemia	1 (3%)	0	0	0	0	0	1 (1%)

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

Treatment related AEs: Treatment related adverse events reported in at least 5% of patients are summarized in Table 3.

The most frequently reported treatment-related AEs (all grades) were nausea (24%), and hyperglycemia/glucose tolerance impaired (22%). The majority of adverse events are mild or moderate. The most frequently reported Grade 3 or higher AE, occurring in 12% of patients overall, was hyperglycemia/glucose tolerance impaired; hyperglycemia improves or resolves in patients following treatment with oral anti-hyperglycemic therapy and/or dose reductions.

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

The most common skin reaction reported in patients treated with EGFR-TKIs is a follicular acneiform eruption. In Study CO-1686-008, rash, irrespective of causality, was reported infrequently (overall 5 patients; 5%) and events were mild. No events of dermatitis acneiform or follicular rash have been reported.

There have been two AEs of pneumonitis. Both were judged related to CO-1686 by the investigator. Both patients recovered when CO-1686 was held and steroids were administered. Neither was re-challenged with CO-1686.

ECGs: ECG results are available for 91 patients. CO-1686 causes an increase in the QTc interval of the ECG, with onset between Day 1 and 15 of treatment. ECG changes are summarized in Table 4. Three (3%) patients have experienced a QTcF > 500 msec, which was managed effectively through dose reduction.

All patients with increased QTc have been asymptomatic. In the overall population, there have been no adverse events suggestive of cardiac arrhythmia (dizziness, presyncope, syncope, sudden death).

There were no electrolyte abnormalities associated with the ECG changes in any of the patients and there was no correlation between the plasma PK parameters of CO-1686 (C_{max}, AUC and C_{12h}) and increase in QTc.

All CO-1686 protocols contain patient selection criteria and specific guidance for the management of patients who develop prolonged QTc.

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

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

Total Daily Dose	< 1800 mg	1800 mg[a]	1000 mg	1250 mg	1500 mg	2000 mg	Total
Formulation	Free base	Free base	HBr	HBr	HBr	HBr	
Frequency	Various[b]	900 mg BID	500 mg BID	625 mg BID	750 mg BID	1000 mg BID	
N	38	19	9	12	9	6	93
Overall	26 (68%)	18 (94%)	5 (55%)	5 (41%)	7 (78%)	5 (83%)	66 (71%)
Blood and lymphatic System Disorders							
Thrombocytopenia	1 (3%)	3 (16%)	0	0	2 (22%)	0	6 (7%)
Gastrointestinal Disorders							
Diarrhea	6 (16%)	6 (32%)	1 (11%)	2 (17%)	1 (11%)	0	16 (17%)
Nausea	7 (18%)	7 (37%)	1 (11%)	2 (17%)	3 (33%)	2 (33%)	22 (24%)
Vomiting	5 (13%)	2 (11%)	1 (11%)	2 (17%)	2 (22%)	0	12 (13%)
General Disorders and Administrative Site Conditions							
Fatigue	8 (21%)	5 (26%)	2 (22%)	1 (8%)	1 (11%)	0	17 (18%)
Investigations							
AST increased	1 (3%)	4 (21%)	0	0	0	0	5 (5%)
ECG QT prolonged	0	2 (11%)	0	0	3 (33%)	2 (33%)	7 (8%)
Metabolism and Nutrition Disorders							
Glucose Tolerance Impaired/Elevated Glucose/ Hyperglycemia	3 (8%)	6 (32%)	3 (33%)	1 (8%)	4 (44%)	3 (50%)	20 (22%)
Musculoskeletal and Connective Tissue Disorders							
Arthralgia	3 (8%)	2 (11%)	0	0	0	0	5 (5%)
Muscle Spasms	3 (8%)	3 (16%)	0	0	0	0	6 (7%)
Myalgia	3 (8%)	4 (21%)	2 (22%)	1 (8%)	0	1 (17%)	11 (12%)
Skin and Subcutaneous Tissue Disorders							
Rash	1 (3%)	1 (5%)	0	0	0	0	2 (2%)

[a]10 patients transitioned to 500 mg BID HBr on availability; [b] 150 mg to 900 mg QD, 100 mg to 600 mg BID, 400 mg TID

Table 4: Electrocardiogram Test Results (QTc - Fridericia)

Total Daily Dose	< 1800 mg	1800 mg	1000 mg	1250 mg	1500 mg	2000 mg	Total
Formulation	Free base	Free base	HBr	HBr	HBr	HBr	
Frequency	Various[a]	900 mg BID	500 mg BID	625 mg BID	750 mg BID	1000 mg BID	
N	37	18	9	12	9	6	91
Post Baseline Results							
QTc > 500 ms							
No	37 (100%)	17 (94%)	7 (78%)	12 (100%)	9 (100%)	6 (100%)	88 (97%)
Yes	0 (0%)	1 (6%)	2 (22%)	0 (0%)	0 (0%)	0 (0%)	3 (3%)
CFB QTc > 30 ms							
No	23 (62%)	7 (39%)	3 (33%)	6 (50%)	2 (22%)	1 (17%)	42(46%)
Yes	10 (27%)	7 (39%)	6 (67%)	6 (50%)	7 (78%)	5 (83%)	41 (45%)
NA	4 (11%)	4 (22%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	8 (9%)
CFB QTc > 60 ms							
No	33 (89%)	14 (78%)	6 (67%)	12 (100%)	7 (78%)	5 (83%)	77 (85%)
Yes	0 (0%)	0 (0%)	3 (33%)	0 (0%)	2 (22%)	1 (17%)	6 (7%)
NA	4 (11%)	4 (22%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	8 (9%)

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

Study CO-1686-016

CO-1686-016 was a 3-part study in healthy male subjects which investigated the PK and safety of single and short course repeat doses of CO-1686 HBr salt. In this study, CO-1686 HBr was administered at single doses up to 1000 mg in the fasted state and at 500 mg BID in the fed state without significant adverse effects.

Following CO-1686 HBr dosing over 4 days at 500 mg BID in a fed state, 3 of 6 healthy male subjects were noted to show asymptomatic increase in QTc on day 4 of dosing which resolved when CO-1686 was discontinued.

Activity of CO-1686

The dose escalation phase of this study is completed and enrolment is ongoing in the dose expansion phase of the study. Although the primary objectives of Phase 1 of Study CO-1686-008 were to evaluate the safety, toxicity and pharmacokinetic profile of CO-1686, encouraging signals of activity have been observed in an EGFR mutation positive patient population previously treated with one of more lines of an EGFR TKI (e.g., erlotinib, gefitinib, afatinib) and chemotherapy. A preliminary analysis of efficacy has been conducted using overall response rate, duration of response, and PFS as efficacy parameters with a cutoff date of 06 March 2014. The efficacy analysis population includes T790M-positive and T790M-unknown patients with measurable disease who have received CO-1686 free base at 900 mg BID or CO-1686 HBr at doses of 500 mg, 625 mg, 750 mg, or 1000 mg BID. Data from the initial dose escalation cohorts using CO-1686 free base indicate that dose levels below 900 mg BID CO-1686 are much less effective than higher doses, are associated with lower plasma exposure, and are therefore likely to be below the therapeutic window.

3.4.1.1 Tumor Responses Associated with CO-1686

Although the data are immature, there is evidence of activity for CO-1686 across the therapeutic doses for patients confirmed as T790M-positive by central testing (Figure 2) with 14 of 22 patients achieving a partial response per RECIST as of the data cut-off date. The ORR in this group of patients is approximately 64% (Table 5) and the disease control rate is approximately 91%. Some of the responses have occurred too recently to allow confirmation. Of the 9 responses that have had the opportunity to be confirmed, 7 (78%) have indeed been confirmed. As shown in Figure 2, 10 of the 14 patients (71%) who achieved a partial response had discontinued from EGFR-directed therapy immediately prior to enrolling in Clinical Study CO-1686-008. Median PFS has not been reached in the T790M-positive subgroup, but will exceed 120 days (Figure 3).

Figure 2: Best Response for Target Lesions in Centrally Confirmed T790M-positive Patients

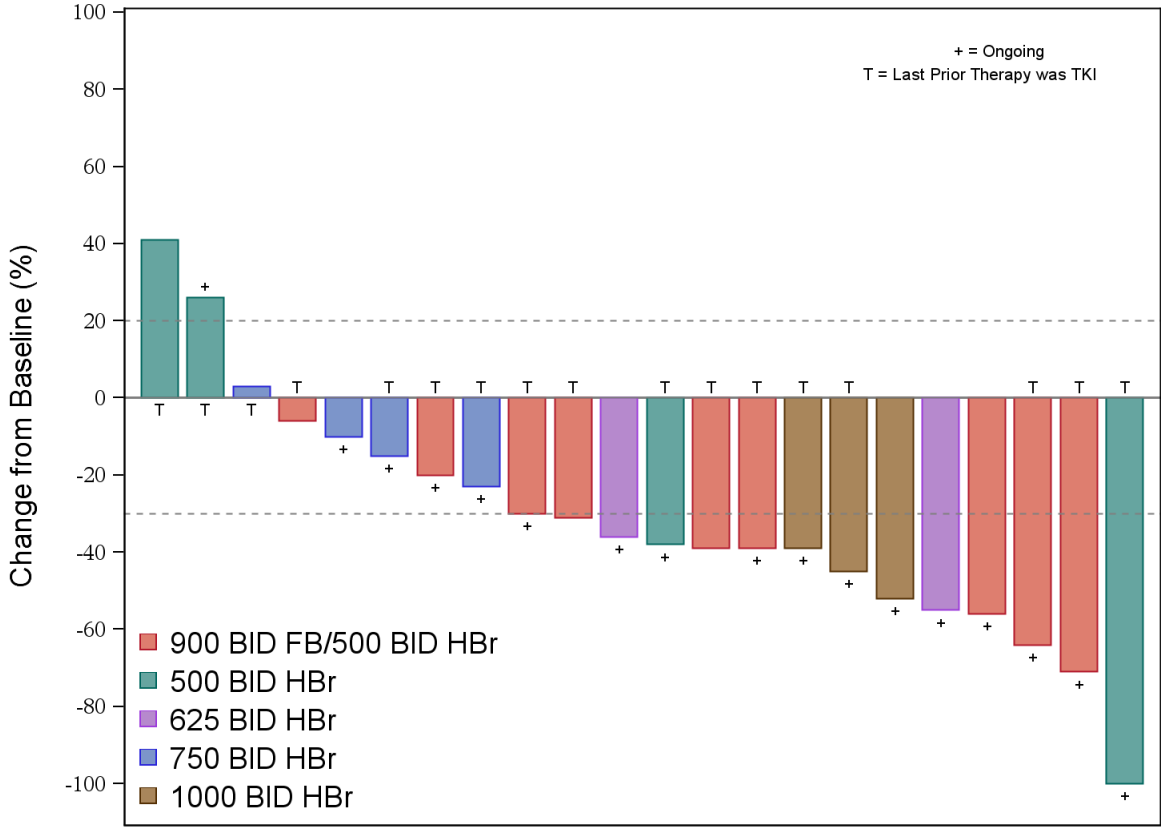


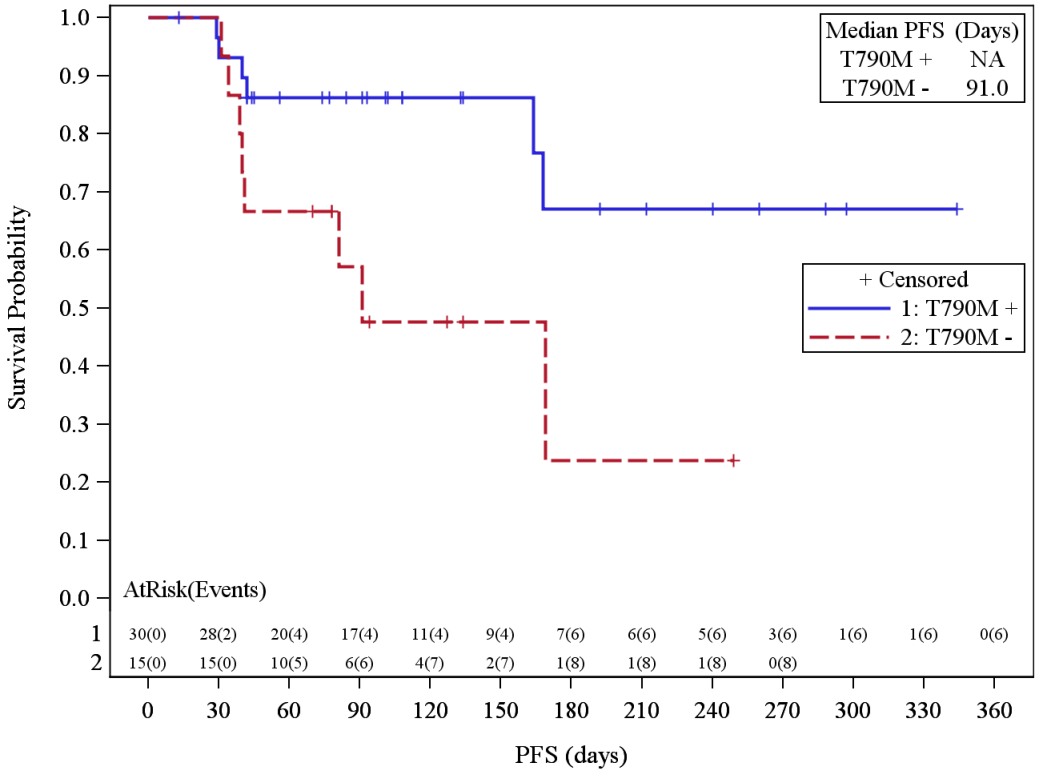
Table 5: Best Response, Objective Response, and Disease Control Rate in T790M-positive Patients

	900 mg BID FB (N = 9)	500 mg BID HBr (N = 4)	625 mg BID HBr (N = 4)	750 mg BID HBr (N = 4)	1000 mg BID HBr (N = 3)	Overall (N = 24)
Best Response [a]						
PR	7 (77.8%)	2 (50.0%)	2 (50.0%)	0 (0.0%)	3 (100.0%)	14 (58.3%)
SD	2 (22.2%)	0 (0.0%)	0 (0.0%)	4 (100.0%)	0 (0.0%)	6 (25.0%)
PD	0 (0.0%)	2 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (8.3%)
End of Cycle 2 scan not yet reached	0 (0.0%)	0 (0.0%)	2 (50.0%)	0 (0.0%)	0 (0.0%)	2 (8.3%)
Objective Response [a, b] (CR, PR)	7 (87.5%)	2 (50.0%)	2 (100.0%)	0 (0.0%)	3 (100.0%)	14 (63.6%)
Disease Control Rate [a, b] (CR, PR, SD)	9 (100.0%)	2 (50.0%)	2 (100.0%)	4 (100.0%)	3 (100.0%)	20 (90.9%)

[a] Data shown are for patients with measurable disease at baseline

[b] Percentage based on patients with non-missing best response

Figure 3: Kaplan-Meier Curves of Treatment Duration by T790M Status for 900 mg BID Free Base and All HBr Patients



3.4.2 *Pharmacokinetics of CO-1686*

In Phase 1 of this study, the PK of single dose and multiple doses of CO-1686 free base capsules demonstrated that C_{max} and $AUC_{0\text{-}24h}$ increased with dose (PK data analyzed for doses escalated from 150 mg once daily to 900 mg once daily and 100 mg twice daily to 900 mg twice daily). Time of occurrence of C_{max} (T_{max}; 1.5 to 4 hours) and terminal half-life ($T_{1/2}$; 3.5 to 5.5 hours) were consistent across doses and there was no accumulation of CO-1686 at any dose.

The single dose PK of 150 mg QD was compared in the fasted and fed state, and it was concluded that a high-fat meal increased the plasma drug concentration at 24 hours post the morning dose (C_{24h};+ 71% to + 300%) and $AUC_{0\text{-}24}$ (+ 44% to > + 110%) with no change in $T_{1/2}$; a lower C_{max} and delayed T_{max} was also seen in a majority of patients.

With CO-1686 free base, moderate inter-and intra-patient PK variability was observed at all doses in the Phase 1 portion of this study. CO-1686 free base is best absorbed at low pH, and its bioavailability is susceptible to factors such as gastric pH and food. These factors may have contributed to the PK variability seen in the study at doses up to 1800 mg daily.

In Phase 1, dose escalation of CO-1686 free base capsules reached 1800 mg daily (900 mg BID). This dose was not the MTD. Dose escalation was stopped with CO-1686 free base at 1800 mg daily with view to continuing dose escalation with a hydrobromide salt formulation of CO-1686 which, based on preclinical data, was anticipated to improve drug dissolution across a wider range of pH and thus increase oral absorption and decrease PK variability.

In healthy volunteers (Study CO-1686-016), C_{max} and $AUC_{0–24}$ 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 to 12 hours post dose with a mean increase of 172% at 12 hours post dose (C_{12h}: –22% to +400%) and a mean increase of 77% in $AUC_{0–24}$ (+10% to 146%) with no change in $T_{1/2}$; a slight mean increase of 12% in C_{max} was observed and a delayed T_{max} was seen in a majority of subjects.

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

In Phase 1 of this study, dose escalation was re-started with CO-1686 HBr at a starting dose of 1000 daily (500 mg BID) as this dose was anticipated to provide exposures comparable to that observed with CO-1686 free base at 900 mg BID. The simulated concentration – time profile at 500 mg BID CO-1686 HBr suggested an AUC_{0-24} range of 11200 to 43200 ng.h/mL, which was comparable to the 95% confidence interval of AUC_{0-24} of 10400 to 42300 ng.h/mL in patients receiving 900 mg BID CO-1686 free base. The C_{min} levels were projected to be 94 to 703 ng/mL, which is comparable to the observed C_{min} of 109 to 1560 ng/mL in patients receiving 900 mg BID CO-1686 free base.

In the Study CO-1686-008, PK data following administration of the HBr salt formulation were available from a total of 44 patients (4 started at 500 mg BID, 10 switched from CO-1686 free base to 500 mg BID HBr, 15 started at 625 mg BID, 9 started at 750 mg BID, and 6 started at 1000 mg BID). CO-1686 HBr showed increased absorption and thus, higher exposure than free base. The median T_{max} was 2.5 to 3.25 hours and $T_{1/2}$ ranged from 1.7 to 4.7 hours, which was slightly shorter than free base in the majority of patients in the ≤750 mg BID cohorts while the $T_{1/2}$ was more similar to free base in the 1000 mg BID cohort. 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 4). Comparative PK were available in 8 patients who originally started CO- 1686 treatment at 900 mg CO-1686 free base BID and then switched to 500 mg CO-1686 HBr BID. Results suggest that CO-1686 HBr delivered a higher exposure, assessed by C_{max}, and lower variability mainly due to a much improved absorption in patients who had low exposure when receiving free base (Figure 5).

Figure 4: Individual CO-1686 AUC_{0-24} on Day 1 Following 500 mg to 1000 mg CO-1686 HBr BID

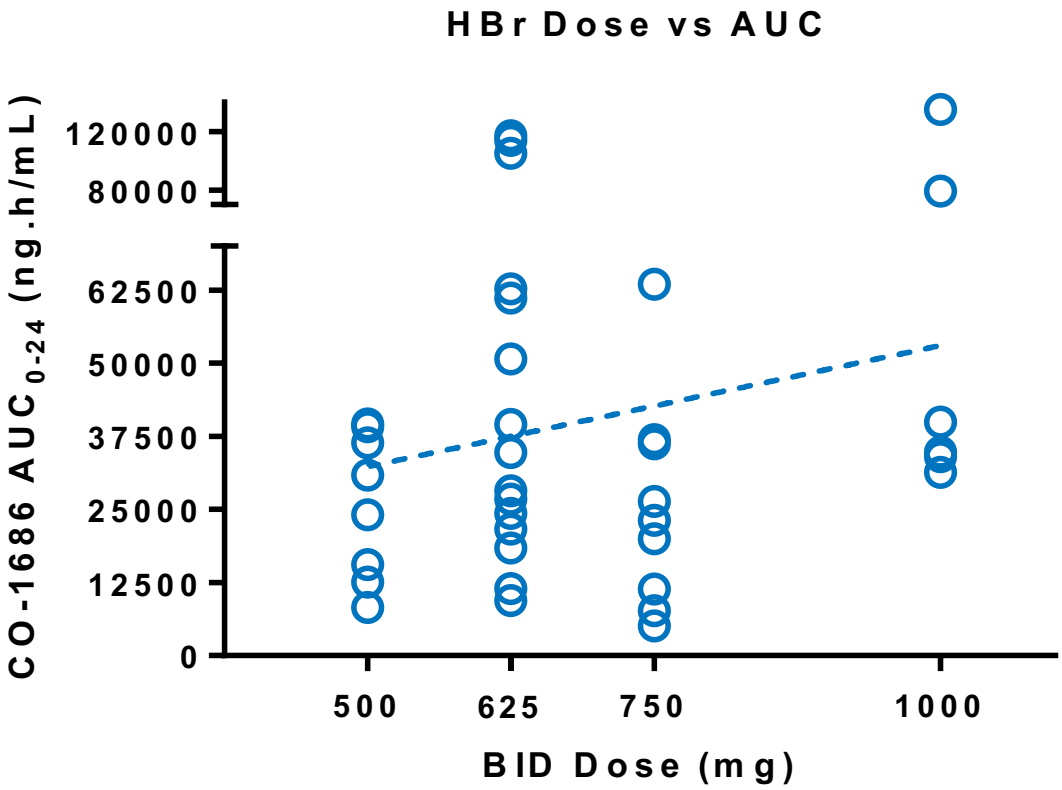
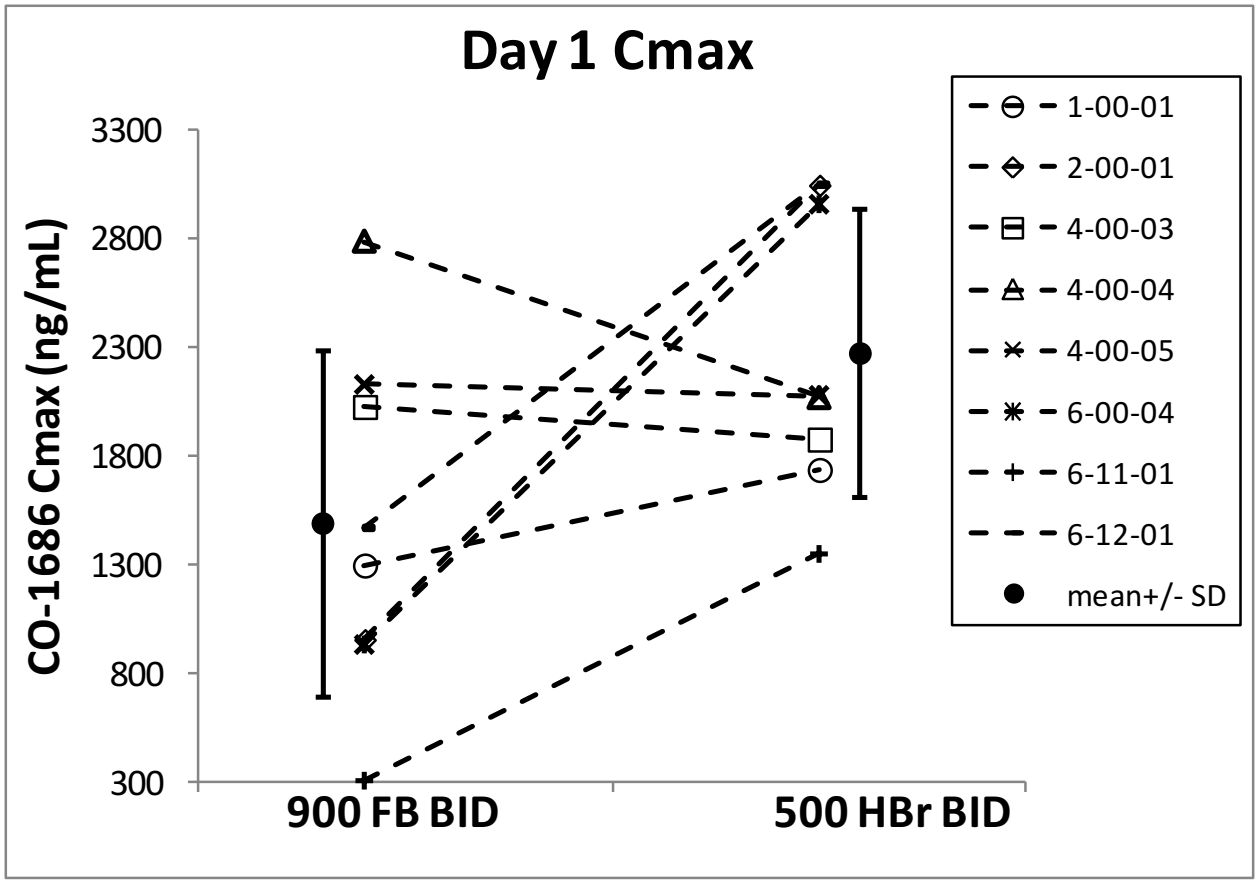


Figure 5: Individual and Mean CO-1686 C_{max} Following a Single Dose of 900 mg CO-1686 Free Base vs. 500 mg CO-1686 HBr



3.5 Rationale for Study and Starting Dose

3.5.1 *Rationale*

As noted previously, 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 activity against activating EGFR mutations and the T790M resistance mutation, and minimal inhibitory activity towards the wild type, CO-1686 may provide an effective therapy for a patient population with few alternative treatment options. Preclinical data point to potential key benefits of treatment with CO-1686:

The drug is active against the T790M EGFR mutation, for which there is currently no approved treatment.

- CO-1686 is WT-sparing; toxicities known to be associated with first generation TKIs, such as rash and diarrhea, will likely not be experienced with CO-1686 treatment.

Initial development will focus on patients with mutant EGFR NSCLC who have failed prior EGFR-directed therapy and have T790M-mediated resistant NSCLC. CO-1686 is being developed with a companion diagnostic to identify patients whose tumors express the activating EGFR mutations as well as the T790M resistance mutation.

3.5.2 *Starting Dose for Phase 1*

The starting dose for the proposed Phase 1 study was calculated according to the Food and Drug Administration's (FDA's) General Guide for Starting Dose Selection for a Cytotoxic Agent in Cancer Patients after evaluation of all toxicity data.

In rats and dogs, the STD_{10} and HNSTD were determined to be 400 and 1000 mg/kg/day, respectively, in the 28-day GLP studies, and these dose levels were used for the purposes of calculating the safe human starting dose.

The rat was the most sensitive species in all the toxicity studies conducted and an appropriate species to use for the calculation of the maximum recommended starting dose for Phase 1. One-tenth of the rat STD_{10} is 240 mg/m^2/day (6.49 mg/kg) or 420 mg/day using 1.75 m^2 for a standard adult human body surface area (Table 6). The dose of 420 mg/day is the maximum starting dose for Phase 1. However, CO-1686 is a poorly soluble compound exhibiting absorption-limited exposure *in vivo* in nonclinical species despite showing a high permeability *in vitro* in Caco-2 cells. In addition, exposure variability was consistently observed in all nonclinical species following PO administration, presumably due to the low solubility of CO-1686 and its pH-sensitive solubility profile. Therefore, taking into account these absorption-related PK uncertainties, the starting dose for the proposed Phase 1 trial is set at 150 mg/day QD, which is approximately one-third of the maximum starting dose allowed by the guideline.

Although the tumor growth inhibition and *in vitro* data are suggestive of increased antitumor activity with BID dosing, a QD schedule will be used for the initial doses in the proposed Phase 1 study to allow determination of the full PK profile. Depending on the time course of exposure in humans, BID dosing may be explored in later dose cohorts.

Based on an evaluation of the nonclinical toxicology and safety pharmacology results, the proposed starting dose for PO administration of CO-1686 to adult advanced cancer patients, 150 mg/day QD, is expected to be tolerated by patients.

Table 6: Estimated Human Starting Doses and Safety Factors Based on Body Surface Area

Species	GLP Toxicology Study Reference Dose (mg/kg/day)	Converted to BSA[a] (mg/m^2)	Applied Safety Factor	Estimated Human MRSD	
				mg/m^{2b}	mg/day[c]
Rat	STD_{10} = 400[d]	2400	10	240[e]	420
Dog	HNSTD = 1000[d]	20,000	6	3333	5832

BSA = body surface area; GLP = Good Laboratory Practice; HNSTD = highest non-severely toxic dose; MRSD = maximum recommended starting dose; STD_{10} = severely toxic dose in 10% of rodents

[a] Conversion for mg/kg to mg/m^2: rat (mg/kg) X 6; dog (mg/kg) X 20.

[b] MRSD = 1/10 STD_{10} (mg/m^2) in rodents or 1/6 HNSTD (mg/m^2) in non-rodents.

[c] Conversion factor from mg/m^2 to mg/day in humans using 1.75 m^2 for a standard adult body surface area.

[d] STD_{10} and HNSTD were determined in rat and dog 28-day GLP toxicology studies.

[e] One tenth of the rat STD_{10} is 240 mg/m^2/day.

3.5.3 *Doses for Phase 2*

A MTD was not reached in Phase 1 for any doses studied with the free-base or HBr CO-1686 formulations. The RP2D of 750 mg BID CO-1686 HBr was selected based on review of the pharmacokinetic, overall safety and preliminary efficacy data available in early 2014, and patients are actively enrolling in cohorts A (later-stage) and B (earlier-stage disease) at 750 mg BID under Amendment 4. Subsequently, as the Phase 1 data matured, the recommended dose was adjusted to 625 mg BID based on robust antitumor activity at lower doses (Figure 2) and anticipated optimal tolerability.

Amendment 6 allowed for the addition of 2 doses levels of CO-1686 (500 mg BID and 625 mg BID) in patients who have progressed on initial EGFR inhibitor therapy (Cohort B), and in patients with later line disease (Cohort A). Patients will no longer enroll in the 750 mg BID dose level for Cohorts A and B, but will be assigned to receive either 625 mg BID or 500 mg BID by the sponsor. Patients who are already receiving 750 mg BID will continue at this dose. Patients will be allocated to Cohorts A and B based on the results of central EGFR testing for T790M status (Therascreen, Qiagen). As it is expected that some patients who test negative for T790M with the central test will have tested positive using local tests, a new cohort (Cohort C, 625 mg BID) has been added to assess activity of CO-1686 in such cases. This last cohort will also be open to patients in whom the central test did not provide an EGFR result because the biopsy specimen was not suitable for analysis by the central lab. Building on the observed efficacy of CO-1686, a more precise estimate of optimum dose will be derived from the augmented cohorts.

4 STUDY OBJECTIVES

4.1 Objectives and Endpoints

Primary, secondary and exploratory objectives and endpoints of Phase 1 (Part 1) are shown Table 7; Primary, secondary and exploratory objectives and endpoints of Phase 2 (Part 2) are shown in Table 8.

Table 7: Phase 1 Primary, Secondary and Exploratory Objectives and Endpoints

Phase 1	
Primary Objectives	**Primary Endpoints**
To evaluate the toxicity profile of escalating doses of CO-1686 and to determine the MTD and RP2D	The incidence of Grade 3 or 4 adverse events (AEs) and clinical laboratory abnormalities defined as dose-limiting toxicities (DLTs)
To characterize the PK profile of CO-1686	PK parameters including area under the curve from time zero to time t (AUC_{0-t}), AUC from time zero to infinity ($AUC_{0-\infty}$), maximum concentration (C_{max}), time to maximum concentration (T_{max}), elimination half-life ($T_{1/2}$), elimination rate constant (k_{el}), volume of distribution at steady state after nonintravenous administration (V_{ss}/F), and total plasma clearance (Cl/F) for CO-1686
Secondary Objective	**Secondary Endpoints**
To characterize the PK profile of CO-1686 after a high-fat breakfast vs in the fasted state	PK parameters C_{max} and AUC for CO-1686 (fasted and fed)
To evaluate the effects of CO-1686 on the QT/QTc interval	Change from baseline in QT/QTc interval
To evaluate tumor response (overall response rate [ORR] + duration of response) of CO-1686	ORR and duration of response per Response Criteria in Solid Tumors (RECIST) Version 1.1
Exploratory Objectives	**Exploratory Endpoints**
To characterize lung-cancer and treatment-related symptoms in patients at baseline and in response to CO-1686 using the Dermatology Life Quality Index, the EORTC QLQ - LC13, and the EORTC QLQ-C30.	Change from baseline in patient-reported outcomes
To explore the concordance of T790M detected in tumor versus that detected in blood.	Concordance of the presence of T790M mutation in blood and tumor tissue samples
To determine if T790M is detectable in urine (optional sampling).	Detection of T790M in urine samples

Table 8: Phase 2 (Part 2): Primary, Secondary and Exploratory Objectives and Endpoints

Phase 2	
Primary Objectives	**Primary Endpoints**
To evaluate tumor response (ORR + duration of response) to CO-1686 in patients with T790M mutation	ORR and duration of response per RECIST Version 1.1 by investigator assessment
Secondary Objectives	**Secondary Endpoints**
To evaluate objective response rate (ORR), duration of response, and progression-free survival [PFS] in patients treated with CO-1686	ORR, duration of response and PFS per RECIST Version 1.1 as determined by independent radiology review (IRR)
To evaluate the toxicity and tolerability of CO-1686	The incidence of AEs, clinical laboratory abnormalities, and ECG abnormalities
To evaluate overall survival (OS), disease control rate (DCR) and progression-free survival [PFS] in patients treated with CO-1686	OS, DCR and PFS per RECIST Version 1.1 as determined by investigator assessment
To determine pharmacokinetics (PK) of CO-1686 using population PK (POPPK) methods and explore correlations between PK, exposure, response, and/or safety findings	Plasma PK parameters for CO-1686 at Cycle 1 Day 1 and Cycle 1 Day 15 for a subset of patients; CO-1686 metabolite profile in the Day 15 plasma samples for a subset of patients; Plasma PK parameters for CO-1686 based on sparse sampling of all patients
To characterize lung-cancer and treatment-related symptoms in patients at baseline and in response to CO-1686 using the Dermatology Life Quality Index, the EORTC QLQ - LC13, and the EORTC QLQ-C30.	Change from baseline in patient-reported outcomes
To evaluate the effects of CO-1686 on the QT/QTc interval	Change from baseline in QT/QTc interval
Exploratory Objectives	**Exploratory Endpoints**
To evaluate clinical benefit of continued CO-1686 treatment following disease progression	Time-to-treatment failure
To explore the concordance of T790M detected in tumor versus that detected in blood	Concordance of the presence of T790M mutation in blood and tumor tissue samples

5 STUDY DESIGN

5.1 Overall Study Design and Plan

This is a two-part, open-label, safety, PK, and efficacy study of oral CO-1686 administered daily in previously treated NSCLC patients who have documented evidence of an activating mutation in the EGFR gene and have failed treatment with an EGFR inhibitor such as erlotinib or gefitinib. Part 1 of the study is the Phase 1 dose-escalation period, Part 2 is the Phase 2 dose-expansion period in patients with T790M positive tumors.

5.1.1 *Screening Period*

Patients will undergo screening assessments within 28 days of 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 ICF and before administration of CO-1686 will also be collected.

5.1.2 *Phase 1*

Dose escalation with CO-1686 free base reached 1800 mg daily. This dose was not the MTD. Dose escalation was re-started with CO-1686 HBr in August 2013, with dose escalation and de-escalation guided by a CRM algorithm in accordance with the rules defined in Section 7.4.1.1. The CRM is described in Appendix C.

Dose Escalation

The dose escalation phase of Part 1 was completed in January 2014. Eligible patients provided tumor tissue for T790M evaluation by the sponsor's central laboratory but enrolment to Phase 1 was irrespective of T790M status. Each patient was treated with oral CO-1686 daily for a 21-day period and underwent assessments for safety (DLTs, AEs, vital signs, clinical laboratory tests, ECOG performance status, ECG and physical examinations) and PK according to the schedule of assessments. All dose escalations were agreed upon between the investigators and the sponsor. The safety monitoring window was 21 days.

As of 30 January 2014, 103 patients with advanced NSCLC have received at least one dose of CO-1686. In the initial stage of the study, 57 patients were treated with CO-1686 administered as free base capsules at doses ranging from 150 mg up to 1800 mg daily. Subsequently, CO-1686 hydrobromide tablets were introduced into the study and 46 patients were treated with CO-1686 administered as hydrobromide tablets. CO-1686-HBr was tested at 500 mg BID, 625 mg BID, 750 mg BID and 1000 mg BID in the dose escalation phase of the study. The MTD was defined as the maximum daily oral dose at which < 33% of patients experience a DLT during Cycle 1 (Safety and PK Assessment Period). Dose escalation evaluation was completed in January 2014 and all doses tested were judged safe (i.e. less than 33% incidence of dose limiting toxicities in Cycle 1). A MTD for free-base or HBr CO-1686 was not reached in the Phase 1 portion of the study.

Transition of Patients on CO-1686 Free Base Capsules to CO-1686 HBr Tablets

Existing patients being treated with CO-1686 free base were transitioned to CO-1686 HBr 500 mg BID once safety evaluation of this dose level was completed. When a patient was transitioned to CO-1686 HBr, the new formulation was to be initiated at Day 1of the cycle and,

preferably, a detailed-hour PK profile on both Days 1 and 15 was to be repeated. At a minimum, however, the pre-dose PK blood samples were to be collected on Day 1 of each treatment cycle of CO-1686 HBr. All Phase 1 patients on freebase were transitioned to CO-1686 HBr by November 2013.

Investigators could transition patients to a lower dose of CO-1686 HBr based on their clinical judgment.

RP2D Selection

The RP2D for evaluation in Phase 2 was to be selected based on overall safety and tolerability, PK, and estimates of efficacious exposures extrapolated from nonclinical data and Phase 1 of the study. The RP2D could or might not be the same as the MTD identified in Phase 1. For example, if the MTD was not reached with a plateau of exposures despite increasing drug dose, or if exposure at the MTD was much higher than the level believed to be required for efficacy, or if subsequent cycles of treatment provided additional insight on the safety profile, then the RP2D **might be** different, though not higher, dose than the MTD.

Additionally, if an MTD was not identified in the dose range expected, a dose that met the tolerability and PK criteria could be selected as the RP2D and dose escalation could continue concurrently to fully explore the exposure and dose relationship. If it is determined that a higher dose in one of the further escalation cohorts is considered likely to be superior to the originally selected RP2D, patients in the Phase 2 or RP2D expansion cohort may be escalated to the new RP2D dose if they meet the intrapatient dose escalation criteria.

Under Amendment 4, the RP2D initially identified in Phase 1 was to be the starting dose for patients enrolled into Phase 2. The RP2D was selected as 750 mg BID based on early efficacy data from the dose escalation portion of the study and patients are actively enrolling in cohorts A (later-stage) and B (earlier-stage disease) at 750 mg BID under Amendment 4. Subsequently, as the Phase 1 data matured, the recommended Phase 2 dose was adjusted to 625 mg BID based on robust antitumor activity at lower doses (Figure 2) and anticipated optimal tolerability. However, since an MTD was not reached in Phase 1 and the small sample size of each Phase 1 cohort, it was not possible to demonstrate a clear dose response for either efficacy or toxicity and consequently the recommended Phase 2 dose at 625 mg BID is an estimation. Amendment 6 allowed for the evaluation of 2 additional doses of CO-1686 (500 mg BID and 625 mg BID) in patients who have progressed on initial EGFR inhibitor therapy and in patients with later line disease. Amendment 7 allowed the sponsor to enroll the RP2D of 625 mg BID before the 500 mg BID dose in order to increase experience with the RP2D to support the ongoing Phase 2 and Phase 3 CO-1686 programs. In addition, Amendment 7 allowed the later-line patient population in Cohort A (more prevalent population) to continue enrollment as long as the earlier line patient population, Cohort B, is open for enrollment. Building on the observed efficacy of CO-1686, a more precise estimate of optimum dose will be derived from these expanded dose levels.

Food-Effect PK Evaluation

The effect of food on CO-1686 PK parameters was assessed in a subset of patients.

PK Evaluation of Once-daily Dosing versus Twice-daily or Three-times-daily Dosing

Dosing was started with QD dosing, and subsequently the effect of BID and three-times-daily (TID) dosing on CO-1686 PK parameters was assessed in a subset of patients.

ECG Monitoring and Effect on QTc

Serial ECG monitoring is performed on all patients in Phase 1, at baseline, on Cycle 1 Day 1 and Cycle 1 Day 15 (prior to dosing and at the multiple time points as described in Table 13 following dosing with CO-1686), and on Day 1 of all subsequent cycles (prior to dosing and at the estimated T_{max} (2 hours) postdose), at the End of Treatment, and as clinically indicated on all patients in order to assess the effect of oral CO-1686 on the QTc interval. All Phase 1 ECGs will be performed on equipment provided by the sponsor (or designee) and reviewed by site personnel and a core/central laboratory.

Triplicate ECG monitoring will be conducted as indicated up to and including Cycle 12 for all patients. For patients who are ongoing at this time and for whom QT has been < 470 ms throughout the study, ECG monitoring may be subsequently reduced to predose evaluation and taken every 3rd cycle thereafter.

Treatment-Extension Period

Upon completion of Cycle 1, Phase 1 patients could participate in an optional Treatment-extension Period, which begins on Day 1 of Cycle 2, if the patient has tolerated the drug, has not progressed and if the treating physician believes it is in the patient's best interest to continue treatment. Oral CO-1686 will be administered daily during this period (21-day cycles) until disease progression, except as described below, unacceptable toxicity, patient or physician request to discontinue, death, or termination of the study.

5.1.3 *Phase 2*

This phase of the study will consist of a screening phase to establish study eligibility and document baseline measurements, an open-label treatment phase, in which patients will receive CO-1686 to ascertain safety and efficacy until protocol-defined disease progression. Each 21-day period of treatment will represent one cycle, with dosing initiated on Cycle 1 Day 1. Eligible patients are those who are confirmed by the sponsor's central laboratory (Cohorts A and B) or by local assessment (Cohort C) to have the T790M mutation in FFPE tumor tissue.

The assessments for patients in each Phase 2 cohort will be identical.

Enrollment into Part 2 was initiated in February 2014 under Amendment 4 when a RP2D of 750 mg BID was selected. This initial RP2D of 750 mg BID was selected based on early Phase 1 efficacy data and two expansion cohorts (Cohorts A and B) are currently enrolling at this dose. As the Phase 1 efficacy data matured, the recommended dose was adjusted to 625 mg BID, and under this amendment patients will no longer enroll in the 750 mg BID dose level for Cohorts A and B, but will be assigned by the sponsor to receive either 625 mg BID or 500 mg BID in these cohorts. Patients who are already receiving 750 mg BID will continue at this dose. Cohort A comprises later-line patients who have previously received one or more prior EGFR TKI, and irrespective of the number and order of previous lines of NSCLC therapy, and who are not eligible for Cohort B. Cohort B comprises earlier-line patients who have had radiologic progression on one prior single agent EGFR TKI for advanced/metastatic NSCLC, and have had

no intervening chemotherapy between EGFR TKI and planned treatment with CO-1686. Amendment 6 expanded the size of cohorts A and B from up to approximately 40 patients each to approximately 190 patients each, and creates 1 additional cohort (Cohorts C with up to 100 patients), in order to assess safety and efficacy at 2 dose levels, and to compare ORR between dose levels. Cohort C (625 mg BID) consists of patients that fulfill eligibility for Cohorts A or B, has signed consent for the study, has a positive local T790M biopsy within 60 days of C1D1 but T790M negative or inadequate test by central laboratory. Patients will be allocated to the 500 mg BID or 625 mg BID dose levels as defined in Section 7.2. Amendment 7 allowed the sponsor to enroll the RP2D of 625 mg BID before the 500 mg BID dose in order to increase experience with the RP2D in order to support the ongoing Phase 2 and Phase 3 CO-1686 programs. In addition, Amendment 7 allowed the later-line patient population in Cohort A (more prevalent population) to continue enrollment as long as the earlier line patient population, Cohort B, is open for enrollment. Patients will be able to enroll in Cohort C as long as the study is recruiting patients for the other cohorts and may contain up to approximately 100 patients.

Separately within each new dose level in Cohorts A and B (500 mg BID and 625 mg BID), the objective response rate will be evaluated in the first 12 patients. Within Cohort C, the objective response rate will be evaluated separately for patients from the 2 patient populations represented by cohorts A and B. If 0 responses are observed in the first 12 patients within each dose level (Cohorts A and B) or patient population (Cohort C) are observed then the respective level or population may be discontinued due to a lack of efficacy. If zero PR or CR responses are observed in 12 patients then there is a high probability that the true objective response rate is less than 20%. In addition to the futility analyses within each cohort, formal safety data reviews will occur following the enrollment of every 50 patients and approximately every 6 months once enrollment is completed and as long as patients remain on treatment. The review committee will include external experts and sponsor personnel. The external experts will include, but not be limited to, the coordinating PIs of the study. The sponsor's reviewers will include the Medical Monitor, Chief Medical Officer, and Biostatistician. The protocol will be amended as appropriate to incorporate additional patient safety monitoring if new safety signals are noted at any review.

If a dose level is closed for further evaluation, ongoing patients in that dose level may be allowed to dose escalate to a higher dose level if they meet the intra-patient dose escalation criteria.

In Phase 2, CO-1686 will be administered daily in 21-day cycles and patients will undergo serial assessments for anti-tumor efficacy, drug safety, and patient reported outcomes. Serial blood sampling for longitudinal quantitative assessment of circulating tumor DNA (ctDNA) will be conducted. For all Phase 2 patients, protocol-specified treatment will continue until there is progression by RECIST Version 1.1, clinical tumor progression or unacceptable toxicity as assessed by the investigator. Patients will undergo serial assessments for anti-tumor efficacy, drug safety, and patient reported outcomes. Serial blood sampling for longitudinal quantitative assessment of ctDNA will be conducted.

Tumor assessments will be performed by the investigative site and scans will be evaluated locally for patient treatment decisions; however, copies of tumor scans will be collected centrally to facilitate independent evaluation for ORR, duration of response, PFS and other assessments as deemed necessary by the sponsor. Following disease progression on CO-1686, patients can consent to participate in an optional additional biopsy before subsequent-line therapy is initiated.

CO-1686 PK Profile at Doses Evaluated in Phase 2 and Metabolite Profiling

A subset of 10 patients at 500 mg BID and 625 mg BID, at a minimum, in Phase 2 will have blood samples collected over 24 hours on Cycle 1 Day 1 and Cycle 1 Day 15 to fully characterize the PK profile of CO-1686 at the dose level. Additionally, at the 625 mg dose level, at a minimum, three of the subset of 10 patients will have additional blood samples collected on Day 1 (predose sample only) and Day 15 (postdose samples) of Cycle 1 for assessment of plasma metabolites. If the three-patient subset is deemed insufficient, additional patients in Phase 2 will have additional blood samples collected for the assessment of plasma metabolites. The CO-1686 parent and metabolite profiling will be conducted at a subset of sites.

All patients in Phase 2 will have trough level PK samples collected on Cycle 1 Day 15, and on Day 1 of all subsequent cycles beginning at Cycle 2 up to and including Cycle 9 (Section 9.8.3.2).

ECG Monitoring and Effect on QTc

In the subset of 10 patients at 500 mg BID and 625 mg BID, at a minimum, for whom a detailed PK profile will be collected in Phase 2, on Cycle 1 Days 1 and 15 ECGs will be monitored over the PK profiling period as outlined in Table 13. Additionally, serial ECG monitoring will be performed: at baseline and on Day 1 of all subsequent cycles (prior to dosing and at the estimated T_{max} (2 hours) postdose), at the End of Treatment, and as clinically indicated in order to assess the effect of oral CO-1686 on the QTc interval.

In all other Phase 2 patients, serial ECG monitoring will be performed: at baseline, on Cycle 1 Day 1, Cycle 1 Day 15 and on Day 1 of all subsequent cycles (prior to dosing and at the estimated T_{max} (2 hours) postdose at these visits), at the End of Treatment, and as clinically indicated. All ECGs will be performed on equipment provided by the sponsor (or designee) and reviewed by site personnel and a core/central laboratory.

Triplicate ECG monitoring will be conducted as indicated up to and including Cycle 12 for all patients. For patients who are ongoing at this time and for whom QT has been < 470 ms throughout the study, ECG monitoring may be subsequently reduced to predose evaluation and taken every 3rd cycle thereafter.

5.1.4 *Treatment Post-progression (Phase 1 and Phase 2)*

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. 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 study assessments including safety assessments, efficacy assessments, QOL administration, and blood collection for biomarker analysis and exploratory research 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.

5.1.5 *End of Treatment and Follow-up (Phase 1 and Phase 2)*

All patients should return to the clinic for End of Treatment assessments 28 (±7) days after the last dose of oral CO-1686 has been administered. During Phase 1 and Phase 2, AEs will be assessed from the time of informed consent through 28 days after the last dose.

5.1.6 *Extension Phase (Phase 1 and Phase 2)*

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 are 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 the study at the discretion of the Principal Investigator in an extension phase.

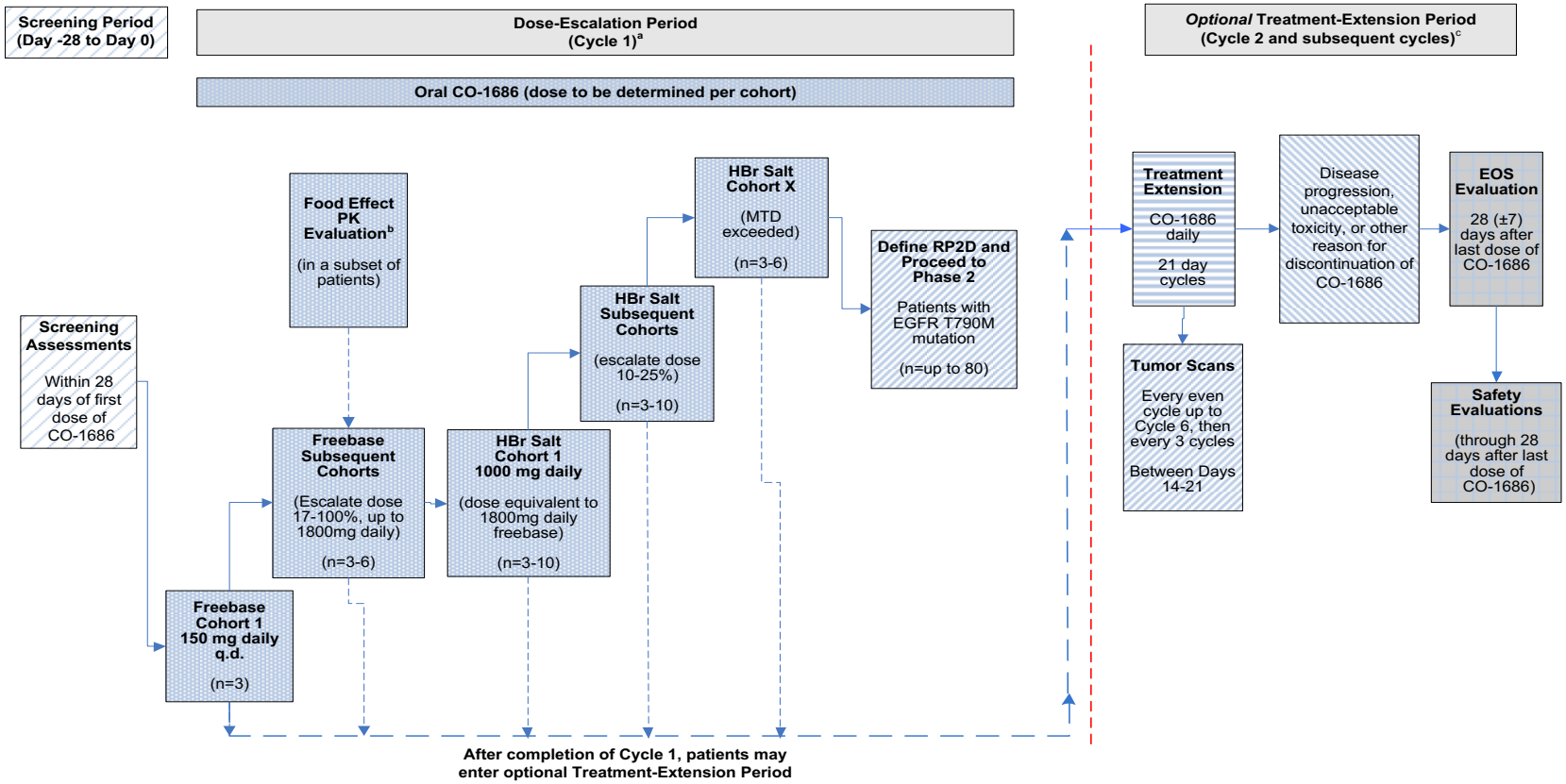
The purpose of this protocol amendment is to add a new Extension Phase to allow patients to continue on study but to avoid unnecessary collection of data that will no longer be analyzed or required for regulatory purposes, whilst maintaining an appropriate level of safety monitoring. A new schedule of assessments for the Extension Phase as well as a complete description of procedures has been provided in Appendix D. This schedule will replace all schedules of assessments in Section 9.1 and should be followed for all patients.

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.

5.2 Study Schema

The study schema in Figure 6 and Figure 7 summarize the treatment designs for Phase 1 and Phase 2 of the study.

Figure 6: Study Schema Phase 1



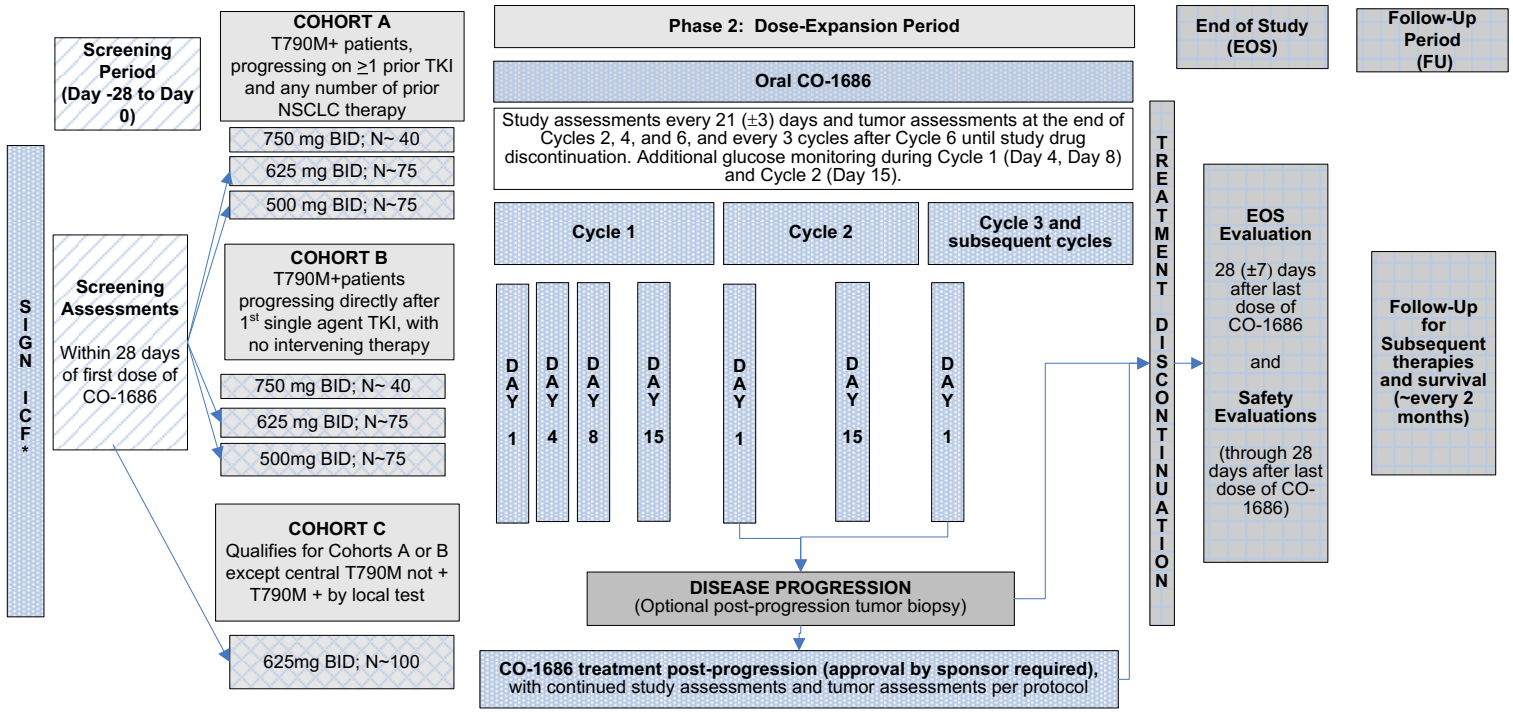
[a] The Dose-escalation Period comprises one cycle of treatment (21-day cycle) within each cohort.

[b] The food-effect PK evaluation will be conducted in a subset of patients (see Table 10 and Table 12).

[c] After completing Cycle 1, patients may enter an optional Treatment-extension Period

Figure 7: Study Schema Phase 2

At Cycle 1 and Cycle 2, patients will undergo assessments on Days 1, 4 (Cycle 1 only), 8 (Cycle 1 only) and 15. Assessments will be on Day 1 of all subsequent Cycles. * ICF signature required before any protocol specific assessments, but signature of ICF does not start screening period timing. The first screening activity performed after ICF signature will begin the 28 day screening period.



5.3 End of Treatment

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

5.4 Two Monthly Follow-up

All patients in Phase 2 will be followed at approximately two monthly intervals to monitor survival status and subsequent NCSLC cancer therapy until death or sponsor decision, whichever comes first. After discontinuation of protocol-specified treatment, subsequent anticancer therapy use will be recorded.

6 STUDY POPULATION

6.1 Number of Patients and Sites

In Phase 1, 57 patients have initiated treatment with CO-1686 free base and approximately 53 patients have been treated with CO-1686 HBr at approximately 8 study sites. Amendment 6 expanded the Phase 2 portion of the study to a total of around 490 patients, with up to approximately 40 patients from both Cohort A and B at the dose level of 750 mg BID and up to approximately 75 patients from both Cohort A and B for each dose level of 500 mg BID and 625 mg BID. Cohort C will also enroll up to approximately 100 patients from approximately 50 study sites. Amendment 7 allowed the sponsor to enroll the RP2D of 625 mg BID before the 500 mg BID dose in order to increase experience with the RP2D to support the ongoing Phase 2 and Phase 3 CO-1686 programs and to increase the total number of patients by approximately 125 patients in Cohort A, for a total of approximately 725 patients (Phase 1 N≈110; Phase 2 N≈605). Cohort A will contain approximately 40 patients for dose level 750 mg BID and up to approximately 275 patients for combined dose levels of 500 mg BID and 625 mg BID. Cohort B will contain approximately 40 patients for dose level 750 mg BID, and up to approximately 150 patients for combined dose levels of 500 mg BID and 625 mg BID. Cohort C will contain up to approximately 100 patients at 625 mg BID dose.

6.2 Inclusion Criteria

All patients enrolling into **either Phase 1 or Phase 2** must meet <u>all</u> of the following inclusion criteria:

1. Histologically or cytologically confirmed metastatic or unresectable locally advanced NSCLC
2. Documented evidence of a tumor with one or more EGFR mutations excluding exon 20 insertion
3. Have undergone a biopsy of either primary or metastatic tumor tissue within 60 days of dosing with study drug and have tissue available to send to the sponsor lab or are able to undergo a biopsy during screening
    a. No change (except for washout or dose adjustment if required to manage adverse effects) in antitumor therapy regimen is allowed between the biopsy and CO-1686 initiation.
4. Life expectancy of at least 3 months
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1
6. Age ≥18 years
7. Adequate hematological and biological function, confirmed by the following screening 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/Independent Ethics Committee-approved Informed Consent Form (ICF) prior to any study-specific evaluation

* In Phase 1 and Phase 2, patients with documented Gilbert's syndrome and conjugated bilirubin within the normal range may be allowed into the study. In this event it will be documented that the patient was eligible based on conjugated bilirubin levels.

Patients enrolling into **Phase 1** must also meet the following inclusion criteria:

- Prior treatment with EGFR-directed therapy (e.g. erlotinib, gefitinib, neratinib, afatinib, or dacomitinib [PF299804]). Prior chemotherapy, including intervening chemotherapy, is allowed.
  - The washout period for an EGFR TKI is a minimum of 3 days
  - The washout period for chemotherapy is a minimum of 14 days
  - Any toxicity related to prior treatment must have resolved to Grade 1 or less

Be willing and able to eat a high-fat breakfast on Day 1 of the study (*only applicable to food-effect cohort).*

Patients enrolling into **Phase 2 Cohort A** must also meet the following inclusion criteria:

- Disease progression confirmed by radiologic assessment while on treatment with EGFR-TKI (e.g. erlotinib, gefitinib, neratinib, afatinib, or dacomitinib). Prior chemotherapy, including intervening chemotherapy before planned initiation of CO-1686, is allowed.
  - The washout period for an EGFR TKI is a minimum of 3 days before planned Cycle 1 Day 1
  - The washout period for chemotherapy is a minimum of 14 days before planned Cycle 1 Day 1
  - Any toxicity related to prior treatment must have resolved to Grade 1 or less by Cycle 1 Day 1
- Documented evidence of T790M mutation in EGFR determined by PCR-based testing of the tumor tissue using the sponsor's central laboratory following disease progression on the most recent EGFR TKI therapy

- Measurable disease according to RECIST Version 1.1.
- Do not qualify for enrolment to Phase 2 Cohort B*

*Patients meeting eligibility criteria for Cohort B must be enrolled into this cohort rather than Cohort A.

Patients enrolling into **Phase 2 Cohort B** must also meet the following inclusion criteria:

- Disease progression confirmed by radiologic assessment while on treatment with the <u>first single agent EGFR</u> TKI (e.g., erlotinib, gefitinib, afatinib, or dacomitinib)
  - EGFR TKI treatment discontinued ≤ 30 days prior to planned initiation of CO-1686
  - The washout period for an EGFR TKI is a minimum of 3 days before planned Cycle 1 Day 1
  - 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 by Cycle 1 Day 1
- Documented evidence of T790M mutation in EGFR as determined by PCR-based testing of tumor tissue using the sponsor's central lab following disease progression on the first single agent EGFR TKI.
- Measureable disease according to RECIST Version 1.1

Patients enrolling into **Phase 2 Cohort C** must also meet the following inclusion criteria:

- Must meet all inclusion criteria of either Phase 2 Cohorts A or B except for documented evidence of T790M mutation using the sponsor's ***<u>central lab</u>***.
- Only patients with evidence of a positive T790M mutation result from a local lab but with an insufficient specimen for central lab analysis (judged by the central lab analysis) or a negative central T790M mutation result from the same biopsy specimen collected within 60 days of treatment with CO-1686.

6.3 Exclusion Criteria

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

1. Documented evidence of an Exon 20 insertion activating mutation 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. Patients with Leptomeningeal carcinomatosis are excluded. Other CNS metastases are only permitted if treated, asymptomatic, and stable (not requiring steroids for at least 4 weeks prior to start of study treatment).
5. Treatment with prohibited medications [e.g., concurrent anticancer therapy including other chemotherapy, radiation treatment or 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
7. Prior treatment with CO-1686 or other drugs that target T790M positive, mutant EGFR with sparing of wild type EGFR, e.g., AZD9291, HM61713, TAS-121
8. Any of the following cardiac abnormalities or history:
   a. Clinically significant abnormal 12-lead ECG, QT interval corrected using Fridericia's method (QT_CF) > 450 msec
   b. Inability to measure QT interval on ECG
   c. Personal or family history of long QT syndrome
   d. Implantable pacemaker or implantable cardioverter defibrillator
   e. Resting bradycardia < 55 beats/min
9. Non-study 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) 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 (e.g., 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 less than 3 days prior to administration of the first dose of CO-1686. If the serum pregnancy results are not available on Day 1, a urine pregnancy test can be performed on Day 1 to confirm that the patient is not pregnant prior to dosing. Both values should be entered in the eCRF. Another serum pregnancy test will be performed at the End of Treatment visit.

Patients of reproductive potential (males and females) must practice double-barrier methods of contraception during treatment and for 12 weeks following the last dose of CO-1686. Adequate contraception is defined as double-barrier protection (i.e., condom plus spermicide in combination with a diaphragm, cervical/vault cap, or intrauterine device). Patients using birth control pills, a birth control patch, or getting injections of hormones to prevent pregnancy must switch to a double barrier method 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 within the 12 week period.

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 Capsule (Used in Phase 1 Only until November 2013)

CO-1686 free base is provided as white, hard capsules for PO administration in two dosage strengths: 50 mg and 150 mg. Each capsule consists of CO-1686 drug substance, Vitamin E polyethylene glycol succinate (Vitamin E TPGS) and polyethylene glycol (PEG 400) filled in a hypromellose capsule shell. Each 50 mg CO-1686 capsule contains approximately 23 IU of Vitamin E in the form of Vitamin E TPGS. Each 150 mg CO-1686 capsule contains approximately 70 IU of Vitamin E in the form of Vitamin E TPGS. Excipients used are generally regarded as safe (GRAS) and commonly used as food additives. The capsules are packaged in blisters. Capsules will be supplied to the study sites by the sponsor. CO-1686 capsules should be stored at room temperature (15°C to 30°C; 59°F to 86°F) in their original packaging.

Child-resistant wallets containing CO-1686 capsules are labeled according to applicable regulations for investigational products. Patients should be advised not to open or crush capsules. Additionally, patients should be advised not to take capsules with visible cracks or leaks. Defective capsules should be returned to the study site.

CO-1686 HBr Tablet (Used in Phase 1 from August 2013 and in All Phase 2 Cohorts)

All patients in Phase 1 who had initiated treatment with CO-1686 free base capsules and were ongoing in the study when CO-1686 HBr 500 mg BID was cleared for safety, were transitioned to CO-1686 HBr. This transition was completed in November 2013 and after this date only CO-1686 HBr tablets are used in this study.

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

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

7.2 Method of Assigning Patients to Treatment Groups

All patients enrolled in the study will receive oral CO-1686. Patients in Phase 2 will receive one of 3 dose levels of CO-1686.

Phase 2 Cohorts A and B were initiated under Amendment 4 at a dose of 750 mg BID and are currently enrolling at this dose. As the Phase 1 efficacy data matured, the recommended dose was adjusted to 625 mg BID, and under Amendment 6, patients were no longer enrolled in the 750 mg BID dose level for Cohorts A and B, but were to be assigned by the sponsor to receive either 625 mg BID or 500 mg BID in Cohorts A and B. Patients who are already receiving 750 mg BID will continue at this dose. Amendment 6 also increased the size of cohorts A and B from up to approximately 40 patients each to approximately 190 patients each (up to approximately 75 patients per dose level of 500 mg BID and 625 mg BID, with up to approximately 40 patients for 750 mg BID), and created 1 additional cohort (Cohort C) with up to 100 patients. Amendment 7 allowed the sponsor to enroll the RP2D of 625 mg BID before the 500 mg BID dose in order to increase experience with the RP2D to support the ongoing Phase 2 and Phase 3 CO-1686 program. Note that, under Amendment 7, as allocation to dose level is not randomized, availability of the central T790M testing result will not be required before enrollment, so long as the following criteria are met:

a. Have undergone a biopsy of either primary or metastatic tumor tissue within 60 days of dosing with study drug and have tissue available to send to the sponsor's lab or are able to undergo a biopsy during screening. No change (except for washout or dose adjustment if required to manage adverse effects) in antitumor therapy regimen is allowed between the biopsy and CO-1686 initiation (Study Inclusion Criterion 3);

   AND

b. Local positive T790M result from biopsy taken at same time as central testing biopsy, with results available for sponsor review before enrollment

7.3 Preparation and Administration of Protocol-Specified Treatment

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

7.3.1 *Phase 1 Requirements for Fasting*

During the initial stages of Phase 1, patients were asked to fast before and after ingestion of CO-1686. Patients who are asked to fast were required to avoid consuming food for 2 hours prior to, and for 2 hours after, ingesting the dose, except as noted below.

On Cycle 1, Day 1 and Day 15, the patient was required to fast for 8 hours prior to and 2 hours after ingesting the dose.

7.3.2 *Phase 1 Requirements for Taking CO-1686 with Food*

During Phase 1, after the PK data for the fed/fasted comparison was available, patients were asked to ingest CO-1686 with food. Patients who are asked to take CO-1686 with food were required to ingest the drug with a meal or within 30 minutes of a meal.

7.3.3 *Food-Effect PK Analysis Fed and Fasted Requirements*

Patients participating in the food-effect PK evaluation were required to take a **single** dose of CO-1686 1 week prior to the start of continuous daily dosing. On this day, patients underwent blood sampling for PK at the time points specified in Section 9.8.3.

Fasted Condition on Day -7

The patient was instructed to arrive for the visit on Day -7 having fasted for at least 8 hours. The patient was instructed to ingest oral CO-1686 with 8 oz. (240 mL) of room temperature water. No food or water was allowed for at least 2 hours postdose.

Fed Condition Day 1

Patients participating in the food-effect PK evaluation were required to consume a high-fat, high-calorie breakfast meal just prior to taking the dose of CO-1686 on Day 1 of the first cycle. On this day, patients will undergo blood sampling for PK at the time points specified in Section 9.8.3.

Following an overnight fast of at least 8 hours, and following performance of all required predose assessments, patients consumed a high-fat (approximately 50% of total caloric content), high-calorie (approximately 800 to 1000 calories total) breakfast meal containing approximately 500 to 600 calories from fat, approximately 250 calories from carbohydrates, and approximately 150 calories from protein, in the clinic. Patients began eating the meal 30 (±5) minutes prior to the planned administration of oral CO-1686. Patients were required to eat this meal in 30 minutes or less; however, oral CO-1686 had to be administered 30 minutes after the start of the meal, regardless of whether the meal was completed or not. Patients ingested oral CO-1686 with 8 oz. (240 mL) of room temperature water. No food was allowed for at least 4 hours postdose. No water was allowed for at least 2 hours postdose.

The breakfast meal was provided by the clinical site or patient. A list of appropriate breakfast meals was provided to clinical sites and patients by the sponsor. An example test meal would be two eggs fried in butter, two strips of bacon (or ham or cheese of similar caloric content), two slices of toast with butter, 4 oz. of hash brown potatoes, and 8 oz. (240 mL) of whole-fat milk. A different breakfast meal to suit specific dietary requirements could be substituted by the clinical site or patient, provided that it has a similar amount of calories and protein, and carbohydrate and

fat content. The nutrient content of the proposed meal must be calculated and submitted to the sponsor (or designee) for review and approval at least 3 days in advance of the patient's scheduled fed day.

7.4 Starting Dose and Dose Modifications of Protocol-specified Treatment

7.4.1 *Phase 1*

7.4.1.1 Dose Escalation

In Phase 1, dose-escalation and de-escalation with CO-1686 HBr was guided by a CRM as described in Appendix C.

The key attributes of this method are:

- The results of the CO-1686 free base dose escalation from this study along with the results of Study CO-1686-016 were used to develop a prior distribution for dose-toxicity relationship that is expected with CO-1686 HBr
- In addition, this study applied a stopping rule to bring the trial to an early halt if the MTD has been established before including the entire sample size of patients for Phase 1
- After completing the toxicity assessment for each patient, the probability that a certain dose level administered was the final RP2D was calculated
- The target toxicity level was set at 33%. The RP2D of this study, if guided by the safety data, was determined to be the next lowest dose below the level at which 33% of patients would experience the DLT

Dose escalation was initiated with three patients enrolled at 500 mg twice daily as this dose had been determined to provide exposure comparable to that of CO-1686 free base at 900 mg BID, which was a dose level that has been cleared for safety.

Following the first cohort, subsequent cohorts of at least three patients were treated at the dose level with an estimated probability of DLT closest to the target toxicity level (33%).

Dose escalation with CO-1686 HBr proceeded as described in Table 9. All dose increments were following discussion and agreement with the investigators.

Table 9: Final Dose Escalation Plan with CO-1686 HBr

Maximum Daily Dose	BID Dosing	% increase in Exposure from Previous Dose
1000 mg daily	500 mg BID	Exposure similar to CO-1686 free base 900 mg BID
1500 mg daily	750 mg BID	50%
2000 mg daily	1000 mg BID	33%
1250 mg daily	625 mg BID	n/a

All dose escalations and de-escalations were agreed upon between the investigators and sponsor. The safety monitoring window was 21 days. Subsequent dose cohorts were opened after at least three patients had completed the 21 day safety monitoring window without a DLT.

There was open enrollment into the study with the following restrictions:

- There could be no more than six patients with unknown DLT information at any time. We refer to the number of patients waiting for DLT information as the "queue."
- Complete DLT information was required for at least three patients at a dose before escalation to a higher dose.

Dose escalation evaluation was completed in January 2014 and all doses tested were judged safe (i.e., less than 33% incidence of dose limiting toxicities in Cycle 1).

7.4.1.2 Maximum Tolerated Dose

The MTD was defined as the maximum daily oral dose at which < 33% of patients experience a DLT during Cycle 1. If a DLT was observed dose escalation was adjusted in accordance with the dose escalation/de-escalation criteria defined in Amendment 4.

7.4.1.3 Dose-limiting Toxicity

DLTs in Phase 1 are defined as any of the following events that occur during Cycle 1 (Safety and PK Assessment Period) in patients enrolled into a DLT evaluable cohort and are assessed by the investigator as probably, possibly or definitively related to CO-1686. Where applicable, events will be classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0.[10] Dose limiting toxicities include:

- Grade 3 or 4 skin eruption, nausea, vomiting, diarrhea or hyperglycemia despite the use of adequate/maximal medical intervention and/or prophylaxis
- Any Grade 4 skin rash/eruption with extensive superinfection requiring IV antibiotics and with life-threatening consequences (e.g., rash acneiform, papulopustular rash, Stevens-Johnson Syndrome)
- Any nonhematological CTCAE Grade 3 or greater AE (except alopecia, nausea, vomiting, diarrhea or hyperglycemia if well controlled by systemic medication)
- ANC $< 0.5 \times 10^9$/L > 5 days duration or febrile neutropenia (i.e., fever > 38.3°C with ANC $< 1.0 \times 10^9$/L)
- Platelets $< 25 \times 10^9$/L or platelets $< 50 \times 10^9$/L with bleeding requiring a platelet transfusion
- Grade 4 anemia (life-threatening consequences, urgent intervention indicated)
- Delayed recovery from toxicity related to CO-1686 treatment that delays scheduled retreatment for > 14 days

7.4.1.4 Definition of DLT-evaluable Patient

In order to be considered evaluable for dose-escalation decisions, a patient in Phase 1 must have:

- Received at least 80% of scheduled doses and have completed Cycle 1, Day 21, without a DLT, or
- Have experienced a DLT in Cycle 1

If a patient withdrew from the study without having met either of these criteria, then an additional patient was to be enrolled in that cohort.

7.4.1.5 Recommended Phase 2 Dose

The RP2D for evaluation in Phase 2 was to be selected based on overall safety and tolerability, PK, and estimates of efficacious exposures extrapolated from nonclinical data and Phase 1 of the study. The RP2D could or might not be the same as the MTD identified in Phase 1. For example, if the MTD was not reached, if exposure at the MTD was much higher than the level believed to be required for efficacy, or if subsequent cycles of treatment provide additional insight on the safety profile, then the RP2D might be a different, although not a higher, dose than the MTD.

Additionally, if an MTD was not identified in the dose range expected, a dose that met the tolerability and PK criteria could be selected as the RP2D and dose escalation could continue concurrently to fully explore the exposure and dose relationship. If it was determined that a higher dose in one of the further escalation cohorts was considered likely to be superior to the originally selected RP2D, patients in the Phase 2 or RP2D expansion cohort could be escalated to the new RP2D dose if they met the intrapatient dose escalation criteria.

Under Amendment 4, the RP2D initially identified in Phase 1 was to be the starting dose for patients enrolled into Phase 2. The RP2D was selected as 750 mg BID based on early efficacy data from the dose escalation portion of the study and patients are actively enrolling in cohorts A (later-stage) and B (earlier-stage disease) at 750 mg BID under Amendment 4. As the Phase 1 efficacy data matured, the recommended dose was adjusted to 625 mg BID, and under Amendment 6 patients will no longer enroll in the 750 mg BID dose level for Cohorts A and B, but will be assigned by the sponsor to receive either 625 mg BID or 500 mg BID in Cohorts A and B. However, since an MTD was not reached in Phase 1, the overall safety profile is similar across all CO-1686 HBr dose ranges, and additional efficacy data indicates viable responses occur across all CO-1686 HBr dose ranges, under Amendments 6 and 7 the dose response relationship of two doses (500 mg BID and 625 mg BID) will be further explored in Phase 2 with the introduction of additional dose levels for patients in earlier stage and later stage of disease.

7.4.1.6 Intrapatient Dose Escalation

Intrapatient dose escalation may be permitted by the sponsor if the maximum drug-related toxicity experienced by the patient is ≤Grade 2 and provided that the dose level to which the patient will escalate has already been cleared at the time of the proposed dose increase. More than one dose escalation may be allowed per patient after approval by the sponsor and the patient has completed 2 cycles at the previous escalated dose without experiencing > Grade 2 drug-related adverse event.

In the event that a patient's dose is escalated, the new dose should be initiated at Day 1 of the cycle and a full PK profile will be repeated. It is preferable that the 24-hour PK is repeated on Days 1 and 15 of the cycle at the higher dose. At a minimum, however, the 24-hour PK should be repeated on Day 15.

7.4.1.7 Dose Expansion at Cleared Dose Levels

Once a dose level had been cleared as described in Section 7.4.1.1, additional patients could be enrolled at a dose lower than the current projected MTD for the purpose of further characterizing pharmacokinetics and efficacy. The data from these additional patients was used to help inform subsequent dose escalation decisions; however, these patients were not formally included in the CRM algorithm.

7.4.2 *Phase 2*

7.4.2.1 Starting Dose

Under Amendment 4, the RP2D initially identified in Phase 1 was the starting dose for patients enrolled into Phase 2. The RP2D selected on completion of dose escalation in Phase 1 was 750 mg BID. As the Phase 1 efficacy data matured, the recommended dose was adjusted to 625 mg BID, and under Amendment 6, patients will no longer enroll in the 750 mg BID dose level for Cohorts A and B, but will be assigned by the sponsor to receive either 625 mg BID or 500 mg BID in Cohorts A and B. Patients who are already receiving 750 mg BID will continue at this dose.

Since an MTD was not reached in Phase 1 and the overall safety profile looked similar across the CO-1686 HBr dose range evaluated, and efficacy was observed across the whole dose range, under Amendments 6 and 7 the dose response relationship of two doses will be further explored in Phase 2 (500 mg BID and 625 mg BID).

If emerging dose-response information supports the termination of a cohort or cohorts, then this decision will be shared with sites. If a cohort is closed for further evaluation, ongoing patients in that cohort may be allowed to dose escalate to a higher dose level if they meet the intra-patient dose escalation criteria.

7.4.3 *Dose Modification Criteria (Phase 1, Phase 2 and the Extension Phase)*

Under Amendment 6, dose reduction steps are allowed for each patient (Phase 1 and Phase 2), with the overall number of dose reduction steps at the investigator's discretion. Dose reductions can occur in 125 mg increments BID from the starting dose (e.g., from 625 mg BID to 500 mg BID). For non-serious adverse events, and upon sponsor approval, a TID dosing regimen may be used to maintain plasma exposure, whilst reducing the peak plasma concentrations which may drive toxicity [e.g., from 625 mg BID (1250 mg total dose/day) to 375 mg TID (1175 mg total dose/day) or 500 mg BID (1000 mg total dose/day) to 250 mg TID (750 mg total dose/day)].

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 to the next lower dose BID and, if persistent, can be further reduced (250 mg increment BID less than starting dose) for subsequent doses if the investigator and the sponsor do not believe treatment discontinuation is required. Re-escalation of dose after resolution of adverse events must be discussed and approved by the sponsor. Dose reductions below 250 mg increment BID less than starting dose must be discussed and agreed with the sponsor before they are implemented.

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

Management of Prolonged QTc

ECGs will be measured throughout the study as described in the protocol. Readings for QT 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 CTCAE 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 the sponsor. After two dose reduction evaluations, 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 and those 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 order to minimize the risk of symptomatic hyperglycemia, the following schedule is recommended:

Fasting glucose will be measured at the following visits: Screening/baseline visit, Cycle 1/Day 1, Cycle 1/Day 4 (±1 day), Cycle 1/Day 8 (±1 day), Cycle 1/Day 15 (±1 day), Cycle 2/Day 1, Cycle 2/Day 15 (±1 day), Cycle 3/Day 1, Cycle 4/Day 1, Cycle 5/Day 1, etc. and End of Treatment visit.

The following guidelines for management of hyperglycemia have been developed by consulting an endocrinologist and based on experience in the Phase 1 study. Whilst the blood glucose thresholds for intervention outlined below should be followed, management of individual patients should be based on local practices and the treating physician's judgment. In all cases, the prescribing information should be followed and maximum approved dose of the anti-hyperglycemic agent should not be exceeded.

1. Additional monitoring outside of per protocol schedule is not needed if fasting glucose is less than 125 mg/dL (< 6.94mmol/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. Tests should be performed at home once a day for 2 weeks, making note of time, fasted/fed state and glucose levels in a monitoring log provided. Patients should

bring this monitoring log to scheduled visits and review with treating physician. If patient observes at home 2 or more fasting glucose measurements > 160 mg/dL (> 8.88 mmol/L) and/or 2 or more random glucose measurements > 200 mg/dL (> 11.01 mmol/L) (or a combination of the two) 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. If glucose > 160 mg/dL (> 8.88 mmol/L) (fasting) or > 200 mg/dL (> 11.01 mmol/L) (random) is confirmed, then start treatment with metformin or anti-hyperglycemic agent of choice (See Figure 8).

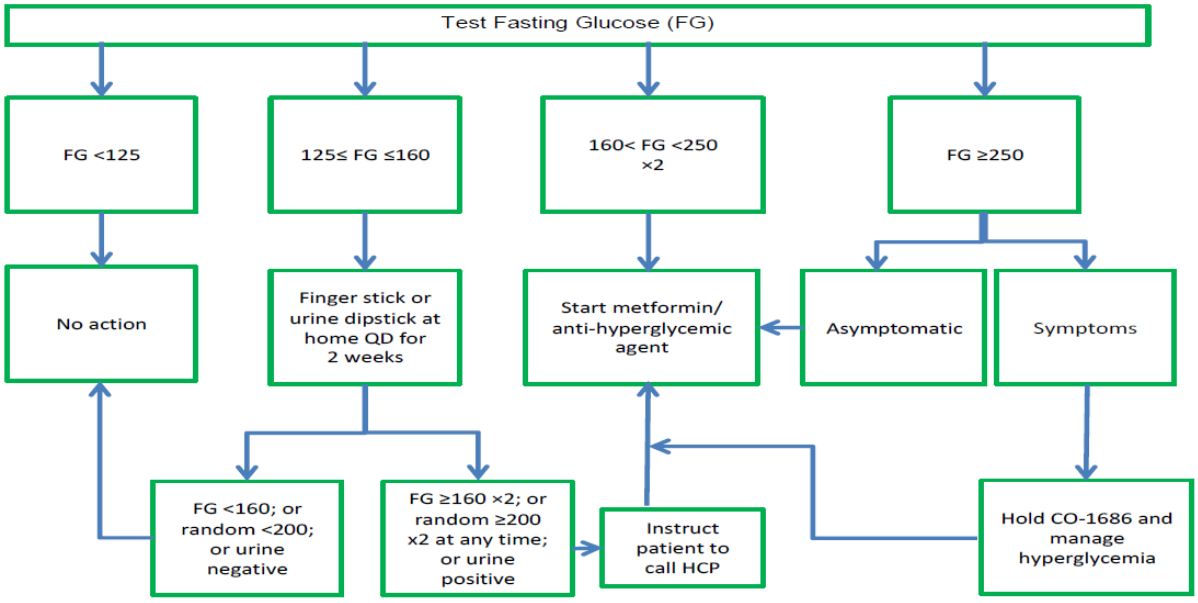
3. If fasting glucose > 160 mg/dL (> 8.88 mmol/L) and < 250 mg/dL (< 13.87 mmol/L) on more than 2 occasions, start metformin or anti-hyperglycemic agent of choice. Patients should perform self-monitoring of blood glucose using finger stick blood testing. Tests should be performed at home once a day, making note of time, fasted/fed state and glucose levels in a monitoring log provided. Patients should bring this monitoring log to scheduled visits and review with treating physician.
4. If fasting glucose ≥250 mg/dL (≥13.87 mmol/L), and the patient is not symptomatic, manage as for step 3 above. If the patient is symptomatic, then hold CO-1686 and bring glucose under control acutely, if necessary using insulin with conversion to metformin or anti-hyperglycemic agent of choice once plasma glucose is controlled. Once patient is asymptomatic and deemed appropriate for additional therapy, CO-1686 may be re-introduced at a reduced dose, with concomitant metformin/anti-hyperglycemic agent of choice. Patients should perform self-monitoring of blood glucose using finger stick blood testing. Tests should be performed at home twice a day, before breakfast and before dinner, making note of time, fasted/fed state and glucose levels in a monitoring log provided. Patients should bring this monitoring log to scheduled visits and review with treating physician.

Use of metformin or other anti-hyperglycemic agents should follow package insert/label. Metformin is contraindicated in patients with renal disease or renal dysfunction, among others, and use should follow package insert and approved label. In order to minimize known GI toxicity associated with metformin use, the extended release form is recommended to improve tolerability.[23] Additional recommendations to avoid GI toxicity with metformin include starting treatment at a reduced dose (500 mg QD) for 72 hours, increasing to 500 mg BID for 72 hours, and only if necessary, and increasing up to 1000 mg BID. If plasma glucose is not adequately controlled after 2 weeks with the regimen outlined above, reduce dose of CO-1686 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 patients treated appropriately.

Figure 8: Guidelines for Management of Hyperglycemia



*Guidelines intend to assist in managing patients that are non-diabetic at study start only. FG = fasting plasma or serum glucose (in mg/dL)

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 wallets or bottles must be accounted for prior to their destruction at the study center. Unused wallets or 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 wallets or 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 oral CO-1686.

7.7 Treatment Compliance

Documentation of dosing will be recorded in a study specific diary card 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 non-compliance is defined as a patient missing > 14 days of medication in a 21 day visit window for 2 consecutive visits. Patients meeting non-compliance

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 oral CO-1686 taken at home in the diary card and to bring the diary card and all unused capsules or 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 electronic case report form (eCRF) and retain the diary card in the patient's medical record.

8 PRIOR AND CONCOMITANT THERAPIES

The investigational product of CO-1686 free base provided high daily doses of vitamin E in the form of vitamin E d-α-tocopheryl polyethylene glycol 1000 succinate (vitamin E TPGS). Patients were required not take supplemental vitamin E, other than a daily multivitamin, while receiving study treatment with CO-1686 free base. These considerations do not apply to patients receiving CO-1686 HBr. Since November 2013, all patients are on CO-1686 HBr.

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 adverse events (e.g., 5HT3 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 QTc changes. The use of such concomitant medications and an appropriate ECG monitoring plan should be agreed between the investigator and the sponsor. Acceptable antiemetics with low potential to affect QTc include phenothiazines and corticosteroids.

All procedures performed (e.g. thoracentesis, etc.) 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 5.1.4 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 Isoenzyme 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. CYP 2D6 appears to play a minor role, but its involvement in CO-1686 metabolism cannot be fully ruled out. Therefore, caution should be exercised with strong inhibitors of CYP2C8 and CYP2D6. For example, CYP2C8

inhibitors such as gemfibrozil, trimethoprim, glitazones, montelukast, and quercetin and CYP2D6 inhibitors such as bupropion, fluoxetine, paroxetine, and quinidine should be avoided.

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

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 oral CO-1686 and requiring concomitant medication with warfarin (Coumadin), nonsteroidal anti-inflammatory drugs (NSAIDs), or clopidogrel, as CO-1686 moderately inhibited CYP2C8, CYP2C9 and CYP2C19 activities *in vitro*. Selection of an alternative concomitant medication with no or minimal enzyme inhibition potential is recommended.

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 oral 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, 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.

9 STUDY PROCEDURES

9.1 Schedule of Assessments

Table 10 summarizes the procedures and assessments to be performed for all Phase 1 patients in all cohorts.

Table 11 summarizes the procedures and assessments to be performed for all patients enrolled in Phase 2 (Cohorts A-C).

Table 12 provides the schedule of PK sampling for all patients in Phase 1 and Phase 2, and the schedule of full PK sampling in a subset of 10 patients at 500 mg BID and 625 mg BID, at a minimum, in Phase 2 and metabolite sampling in a subset of 3 of these Phase 2 patients at the 625 mg BID dose level.

Table 13 provides the schedule of PK sampling and ECG collection in Phase 1 and for the subset of Phase 2 patients participating in the RP2D (625 mg BID) detailed PK profiling.

All procedures and assessments are to be completed within ±1 day of the scheduled time point and are synchronized with administration day of oral CO-1686 treatment unless otherwise indicated. NOTE: With the approval of this protocol version, all ongoing patients, both Phase 1 and Phase 2, will be treated on the Extension Phase of the study and should follow the schedule of assessments provided in Appendix D.

Table 10: Protocol CO-1686-008 Schedule of Assessments – Phase 1: All Cohorts

Procedure[b]	Screening Period	Treatment Period				End of Treatment
		Dose-Escalation Period (Daily Dosing)[a]			Optional Treatment-Extension Period	
	Day -28 to Day 0[c]	Food-Effect Only Cycle 1 Day -7[d]	Cycle 1 Day 1[e]	Cycle 1 Days 8 and 15	Cycles 2+ Day 1[f]	
Informed Consent	X					
Medical/Oncology History	X					
Physical Examination	X	X	X	X[h]	X	X
ECOG Performance Status	X	X	X		X	X
Vital Signs[g] and Weight	X	X	X	X	X	X
Prior/Concomitant Medications and Procedures	X	X	X	X	X	X
Contraceptive Counseling[i]	X					X
Serum Pregnancy Test[j]	X					X
Hematology, Including Reticulocytes[k]	X	X	X	X	X	X
Fasting Serum Chemistry[l]	X	X	X	X	X	X
Urinalysis[m]	X					
Tumor Scans Including Brain Imaging[n]	X				X	X
Tumor Biopsy[o]	X					X
Blood for biomarker/EGFR Mutational Testing and exploratory research[p]	X		X	X	X	X
Blood for CYP Evaluation (Optional Sampling)			X			
Adverse Events[q]	X	X	X	X	X	X
CO-1686 Dispensing / Administration		X[r]	X[r]	X	X	
Patient Diary[s]			Dispense diary	X	X	X
ECG Assessment[t]	X		X	X	X	X
Quality of Life Questionnaires[u]			X		X	X
High-fat Breakfast[v]			X			
Plasma PK and Serum AAG Samples (Table 12)		X	X	X	X	

Optional: Urine collection for biomarker research [w]			X		X	X

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

a = CO-1686 will be administered daily for the 21-day treatment period.

b = Unless specified, procedure is completed ±1 day of scheduled time point and is synchronized with administration day of CO-1686.

c = The screening period for patients participating in the food-effect evaluation will be between Days -28 to Day -8.

d = Applies to patients participating in food-effect evaluation only.

e = Procedures required on Day 1 of Cycle 1 may be omitted if completed ≤3 days earlier during the screening period.

f = Starting on Day 1 of Cycle 2, patients may enter an optional Treatment-extension Period, during which CO-1686 is administered daily until the patient experiences disease progression, except as described in Section 5.1.4, unacceptable toxicity, request by patient or physician to discontinue treatment, death, or termination of the study by the sponsor.

g = Vitals (blood pressure, pulse, temperature) should be taken predose on drug administration days

h = Physical examination is limited/targeted on Days 8 and 15.

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

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

k = 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 analyzed by a local laboratory and must be reviewed by the investigator prior to start of CO-1686 administration. Additional tests may be performed at the investigator's discretion.

l = Includes total protein, albumin, creatinine, BUN or urea, total bilirubin, alkaline phosphatase, ALT, AST, **fasting** glucose, sodium, potassium, chloride, CO_2, calcium, phosphorus, total cholesterol ≤28 days prior to first day of dosing. Glucose must be measured following an 8 hour fast (no food or liquid other than water) at the screening and the start of every subsequent cycle. Hemoglobin A1c will be measured at screening and on Day 1 of every other cycle, starting at Cycle 3 while the patient is on study. Samples may be analyzed by local laboratory.

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

n = Tumor scans obtained within 28 days prior to Cycle 1, Day 1, may be used as the baseline scans. Scans will include the pelvis, chest, and abdomen (preferably CT scans with appropriate slice thickness per RECIST Version 1.1). Other studies (MRI, 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 study. Brain imaging is required at baseline and must be repeated at follow-up tumor assessments for patients with brain lesions. Scans to be performed at screening; at the end of Cycles 2, 4, and 6 (between Days 14-21); every 3 cycles after Cycle 6 (between
Days 14-21); and End of Treatment. Tumor scans do not need to be repeated at End of Treatment if < 2 weeks since last scan or the patient had disease progression

at the last scan. If an initial CR or PR is noted at Cycle 7 or beyond, confirmatory scans must be performed 4-6 weeks 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 6–8 weeks.

o = Biopsy of either primary or metastatic tumor tissue. A corresponding blood specimen will be obtained prior to tumor specimen collection. If biopsy was performed within 28 days of Cycle 1, Day 1, and no intervening treatment was given, a repeat biopsy is not required if an FFPE tumor tissue block from the recent biopsy can be provided to the sponsor during the Screening period. In this case, the blood specimen should be taken at least 7 days AFTER the biopsy was performed. At progression and/or End of Treatment, an optional tumor biopsy can be performed if the patient provides additional written consent.

p = Blood sampling for biomarker/EGFR mutational testing and exploratory research will be collected at Screening (prior to biopsy, or at least 7 days AFTER the biopsy was performed); predose on Days 1, 8 and 15 of Cycle 1 and Day 1 of Cycle 2 and beyond; and at the End of Treatment visit. Refer to the Laboratory Manual for blood processing requirements and handling instructions.

q = 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.

r = For the patients participating in the food-effect evaluation only, they will be instructed to fast for at least 8 hours prior to arrival at this visit, and to fast for 4 hours after dosing.

s = Patient diaries should be collected and reviewed for compliance.

t = Anytime during screening; On Cycle 1 Day 1, Cycle 1 Day 15 and Day 1 of each subsequent cycle and End of Treatment as described in Table 13.

u = Quality of Life Questionnaires, the EORTC QLQ C30 and LC13 and the Dermatology Life Quality Index, should be collected from the patient prior to dosing at Cycle 1, Day 1; then on Day 1 of Cycles 3, 5, and 7. After Cycle 7, questionnaires will be collected every 3 cycles (on Day 1 Cycles 10, 13, 16, etc.), and at End of Treatment

v = Patients in the food-effect cohort must start a high-fat breakfast (and complete within) 30 minutes prior to dosing with oral CO-1686.

w = Urine collection for biomarker research is optional and requires additional consent. Instruct patients to collect 100 mL of the first morning void on Day 1 of Cycles 1 – 6 and at End of Treatment. Patients will bring urine samples to the clinic during their regularly scheduled visits on the day of collection. Sample collection containers and instructions will be provided. Refer to the Laboratory Manual for sample handling and shipping instructions.

Table 11: Protocol CO-1686-008 Schedule of Assessments – Phase 2: All Patients

	Screening	Treatment Period Phase 2 – Dose-Expansion Period (Daily Dosing)[a]						Post- Treatment	
Procedure[b]	**Day -28to Day -1**	**Cycle 1 Day 1[c]**	**Cycle 1 Day 4 ±1 day**	**Cycle 1 Day 8 ±1 day**	**Cycle 1 Day 15**	**Cycle 2 and Beyond Day 1**	**Cycle 2 Day 15 ±1 day**	**End of Treatment (28±7 days after last dose)**	**Follow-Up Every 8 ±1 weeks after EOT**
Informed Consent*	X								
Medical/Oncology History	X								
Physical Examination	X	X			X	X		X	
ECOG Performance Status	X	X				X		X	
Vital Signs[d] and Weight	X	X			X	X		X	
Prior/Concomitant Medications and Procedures	X	X			X	X		X	
Contraceptive Counseling[e]	X							X	
Serum Pregnancy Test[f]	X							X	
Hematology, Including Reticulocytes[g]	X	X			X	X		X	
Fasting Serum Chemistry[h]	X	X	Fasting glucose only	Fasting glucose only	X	X	Fasting glucose only	X	
Urinalysis[i]	X								
Tumor Scans, Including Brain Imaging[j]	X					X		X	
Tumor/Metastasis Biopsy for T790M Status[k]	X							X	
Blood for biomarker/EGFR Mutational Testing and exploratory research [l]	X	X			X	X		X	
Blood for CYP Evaluation (Optional Sampling)		X							
Adverse Events[m]	X	X			X	X		X	

Procedure[b]	Screening	Treatment Period Phase 2 – Dose-Expansion Period (Daily Dosing)[a]						Post- Treatment	
	Day -28to Day -1	Cycle 1 Day 1[c]	Cycle 1 Day 4 ±1 day	Cycle 1 Day 8 ±1 day	Cycle 1 Day 15	Cycle 2 and Beyond Day 1	Cycle 2 Day 15 ±1 day	End of Treatment (28±7 days after last dose)	Follow-Up Every 8 ±1 weeks after EOT
CO-1686 Dispensing / Administration		X			X	X			
Patient Diary[n]		Dispense Diary			X	X		X	
ECG Assessments[o]	X	X			X	X		X	
Quality of Life Questionnaires[p]		X				X		X	
Plasma PK and Serum AAG Samples (Table 12)		X			X	X			
Metabolite Profiling (Table 12)		X			X				
Optional: Urine collection for biomarker research [q]		X				X		X	
Subsequent Therapies for NSCLC								X	X

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

[*] = ICF signature is required before any protocol specific assessments, but signature of ICF does not start screening period timing. The first screening activity performed after ICF signature will begin the 28 day screening period (not including biopsy).

[a] = CO-1686 will be administered daily at doses specific for cohorts A-C for the 21-day treatment period.

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

[c] = Procedures required on Day 1 of Cycle 1 may be omitted if completed ≤3 days earlier during the screening period.

[d] = Vital signs (blood pressure, pulse, and temperature) taken predose on drug administration days.

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

	Screening	Treatment Period Phase 2 – Dose-Expansion Period (Daily Dosing)[a]						Post- Treatment	
Procedure[b]	**Day -28to Day -1**	**Cycle 1 Day 1[c]**	**Cycle 1 Day 4 ±1 day**	**Cycle 1 Day 8 ±1 day**	**Cycle 1 Day 15**	**Cycle 2 and Beyond Day 1**	**Cycle 2 Day 15 ±1 day**	**End of Treatment (28±7 days after last dose)**	**Follow-Up Every 8 ±1 weeks after EOT**

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

[g] = 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 analyzed by a local laboratory and must be reviewed by the investigator prior to start of CO-1686 administration. Additional tests may be performed at the investigator's discretion.

[h] = Includes total protein, albumin, creatinine, BUN or urea, total bilirubin, alkaline phosphatase, ALT, AST, **fasting** glucose, c-peptide, sodium, potassium, chloride, CO_2, calcium, magnesium, phosphorus, total cholesterol ≤28 days prior to first day of dosing. Glucose must be measured following an 8 hour fast (no food or liquid other than water). Hemoglobin A1c will be measured at screening and on Day 1 of every other cycle, starting at Cycle 3 while the patient is on study. Samples should be analyzed by local laboratory. C-peptide will be measured at screening, and Day 1 of every cycle.

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

[j] = Tumor scans obtained within 28 days prior to Cycle 1, Day 1, may be used as the baseline scans. Scans will include the pelvis, chest, and abdomen (preferably CT scans with appropriate slice thickness per RECIST Version 1.1), using the same methods throughout the study that were used to detect lesions at baseline. Other studies (MRI, X-ray) may be performed if required. Brain imaging is required at baseline and must be repeated at follow-up tumor assessments for patients with known brain lesions only. Scans to be performed at screening; at the end of Cycles 2, 4, and 6 (between Days 14-21); every 3 cycles after Cycle 6 (between Days 14-21); and End of Treatment. Tumor scans do not need to be repeated at End of Treatment if < 2 weeks since last scan or the patient had disease progression at the last scan. If an initial CR or PR is noted at Cycle 7 or beyond, confirmatory scans must be performed 4-6 weeks 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 6–8 weeks.

[k] = Biopsy of either primary or metastatic tissue to determine EGFR T790M status for enrollment eligibility, and for the development of a validated tissue-based EGFR T790M test. If a biopsy was performed within 60 days of Cycle 1, Day 1, and no intervening treatment was given, a repeat biopsy is not required provided adequate tumor tissue is available for EGFR mutation testing by the sponsor's central laboratory testing to determine eligibility. At progression and/or End of Treatment, an optional tumor biopsy can be performed if additional patient consent is obtained. All tumor tissue will be processed locally as formalin-fixed paraffin-embedded (FFPE) tissue. Patients with a negative or insufficient result by central laboratory may be enrolled into Cohort C if they have a positive T790M result from a local test of the same biopsy. Assessments performed prior to patient signing informed consent are acceptable only if confirmed to have been standard of care..

[l] = Blood sampling for biomarker/EGFR mutational testing and exploratory research will be collected at Screening (prior to biopsy, or at least 7 days AFTER the biopsy was performed); predose on Days 1 and 15 of Cycle 1 and Day 1 of Cycle 2 and beyond; and at the End of Treatment visit. Refer to the Laboratory Manual for blood processing requirements and handling instructions.

[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.

Procedure[b]	Screening	Treatment Period Phase 2 – Dose-Expansion Period (Daily Dosing)[a]						Post- Treatment	
	Day -28to Day -1	Cycle 1 Day 1[c]	Cycle 1 Day 4 ±1 day	Cycle 1 Day 8 ±1 day	Cycle 1 Day 15	Cycle 2 and Beyond Day 1	Cycle 2 Day 15 ±1 day	End of Treatment (28±7 days after last dose)	Follow-Up Every 8 ±1 weeks after EOT

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

[o]=Phase 2 patients not taking part in detailed PK profiling - anytime during screening, predose and approximately 2 hours postdose on Cycle 1 Day 1 and Cycle 1 Day 15, Predose and approximately 2 hours postdose on Day 1 of each Subsequent Cycle, and at End of Treatment, any time after treatment is discontinued.

For the subset of Phase 2 patients taking part in the detailed full PK profiling - anytime during screening; On Cycle 1 Day 1, Cycle 1 Day 15 and Day 1 of each subsequent cycle and End of Treatment as described in Table 13

[p] = Quality of Life Questionnaires, the EORTC QLQ LC13 and the Dermatology Life Quality Index, should be collected from the patient prior to dosing at Cycle 1, Day 1; then on Day 1 of Cycles 3, 5, and 7. After Cycle 7, questionnaires will be collected every 3 cycles (on Day 1 Cycles 10, 13, 16 etc.), and at End of Treatment.

[q] =Urine collection is optional and requires additional consent. Instruct patients to collect 100 mL of the first morning void on Day 1 of Cycles 1 – 6 and at End of Treatment. Patients will bring urine samples to the clinic during their regularly scheduled visits on the day of collection. Sample collection containers and instructions will be provided. Refer to the Laboratory Manual for sample handling and shipping instructions

Table 12: Protocol CO-1686-008 Schedule of Pharmacokinetic Sampling and Metabolite Sampling – Phase 1 and 2

	For Phase 1 Food-Effect PK Evaluation Only	All Phase 1 Patients and Phase 2 - Subset of Patients providing full PK profile (at least 10 Patients at 500 mg BID and 625 mg BID)				Phase 2 All Other Patients		
	Prior to Cycle 1	Cycle 1			Cycles 2+ (Phase1) (up to and including Cycle 9- Phase 2 – subset of patients only)	Cycle 1		Cycles 2+ (up to and including Cycle 9)
Procedure	**Day -7**	**Day 1**	**Day 8 (Phase 1 only)**	**Day 15**	**Day 1**	**Day 1**	**Day 15**	**Day 1**
Pre-dose Plasma PK and AAG Serum Samples	X[a]	X[a]	X[b]	X[b]	X[a]		X[b]	X[a]
Post –dose Plasma PK Samples and AAG Serum Samples	X[c]	X[c]		X[c]				
Plasma Samples for Metabolite Profiling -		X[d]		X[e]				

[a] = Any time prior to dosing

[b] = 5-10 min prior to dosing

[c] = at 15 (±2) min, 30 (±3) min, 1 hr (±5 min), 1.5 hr (±5 min), 2.5 hr (±5 min), 4 hr (±15 min), 6 hr (±15 min), 8 hr (±15 min), 10 hr (±30 min), and 24 hr (±30 min) after dosing

[d] = In a minimum of 3 patients of the 10 patient subset in Phase 2 at 625 mg BID, an additional 2 mL sample will be collected prior to CO-1686 administration. This will serve as the baseline sample for subsequent profiling of CO-1686 circulating metabolites

[e] = In a minimum of 3 patients of the 10 patient subset in Phase 2 at 625 mg BID, an additional 2 mL samples will be collected postdose at 30 (±3) min, 1.5 hr (±5 min), 4 hr (±15 min), 8 hr (±15 min), and 24 hr (±30 min) postdose . This will be the on study sample for profiling of CO-1686 circulating metabolites

Table 13: Time Points for Pharmacokinetic and 12-Lead ECGs (Triplicate) Evaluations

	Phase 1 and Phase 2 Subset of Patients Participating in full PK Profiling at 625 mg BID			**Other Phase 2 Patients**			**All Patients**
	Cycle 1		*Cycle 2+*	*Screening*	*Cycle 1*	*Cycle 2+*	*EOT*
	Blood for PK	**12-Lead ECGs (Triplicate)**					
Time Point	*Day 1 & Day 15*	*Day 1 & Day 15*	*Day 1of Cycle*	*Screening (all patients)*	*Day 1 & Day 15*	*Day 1of Cycle*	*EOT*
Predose	X	X[a]	X[a]	X	X[a]	X[a]	X[e]
15 min	X						
30 min	X						
1h	X	X[b]					
1.5h	X						
2h		X[c]	X[c]		X[c]	X[c]	
2.5h	X						
4h	X	X[b]					
6h	X						
7h		X[d]					
8h	X						
10h	X	X[b]					
24h	X	X[b]					

[a] 12-lead ECG taken (in triplicate) prior to dosing
[b] 12-lead ECG taken (in triplicate) 10 minutes prior to PK sampling time point
[c] 12-lead ECG taken (in triplicate) 2h postdose
[d] 12-lead ECG taken (in triplicate) 7h postdose
[e] 12-lead ECG taken (in triplicate) anytime within 28 days of treatment discontinuation
Note 1: Screening ECGs are required in triplicate for all patients.
Note 2: Triplicate ECG monitoring will be conducted as outlined above up to and including Cycle 12. For patients who are ongoing at this time and for whom QT has been < 470 ms throughout the study, ECG monitoring may be subsequently reduced to predose evaluation and taken every 3rd cycle thereafter. If Patients do not meet this criteria, ECG evaluation should continue on Day 1 of each Cycle as defined above.

9.2 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 of oral CO-1686. 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, and any surgical procedures.
- Documented evidence of a tumor with one or more EGFR mutations excluding exon 20 insertion.
- Biopsy of primary or metastatic lesions to provide FFPE tumor tissue for EGFR mutational testing and companion diagnostic kit development within 60 days of study drug dosing. To ensure adequate viable tumor tissue is obtained, image-guided biopsies should be achieved with 18- to 20-gauge cutting needles to provide 1 to 3 cores measuring 1 to 1.5 cm in length. Tumor samples will be processed locally to yield FFPE tissue blocks. Entire FFPE blocks must be submitted to satisfy regulatory requirements for development of the companion diagnostic. Blocks will be returned upon request if required for legal or medical treatment purposes. EGFR T790M status testing for eligibility for Phase 2 will be done by the sponsor's central lab.

  Patients with a negative or insufficient result by central laboratory may be enrolled into Cohort C if they have a positive T790M result from a local test of the same biopsy.
- Blood sampling for biomarker/EGFR mutational testing and exploratory research. Matched blood samples are required and should be collected prior to the biopsy procedure, if possible. Detailed sample handling instructions are provided in the Laboratory Manual.
  - If a biopsy was performed within 60 days of Cycle 1/Day 1, 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. In this case, blood sampling should be taken at least 7 days AFTER the biopsy was performed.
- Physical examination by body system, height, and weight.
- ECOG performance status.
- Vital signs (blood pressure, pulse, and temperature).
- Prior and concomitant medications and procedures.
- Contraceptive counseling.
- Prior treatment for NSCLC.
- 12-lead ECG (in triplicate, 10-sec tracings > 2 min apart).
- Hematology [hemoglobin, hematocrit, white blood cells (WBC) and differential (with ANC), and platelet count] and reticulocyte count ≤14 days prior to the first day of dosing.

- **Fasting** serum chemistry [total protein, albumin, creatinine, c-peptide, blood urea nitrogen (BUN) or urea, total bilirubin, alkaline phosphatase, ALT, AST, fasting glucose, sodium, potassium, magnesium, chloride, CO_2, calcium, and phosphorus], total cholesterol and hemoglobin A1c ≤ 28 days prior to the first day of dosing. Fasting is defined as an 8 hour fast (no food or liquid other than water).
- Serum pregnancy test (by local laboratory) ≤ 3 days prior to the first day of dosing for women of childbearing potential. If the serum pregnancy test results are not available on Day 1, a urine pregnancy test can be performed on Day 1 to confirm that the patient is not pregnant prior to dosing. Both values should be entered in the eCRF.
- 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, abdomen, and pelvis. 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 (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.
    - Patients with known brain metastases or brain lesions detected at baseline are required to repeat brain imaging as part of the follow-up tumor assessments. The same methods used to detect brain lesions at baseline are to be used to follow the same lesions throughout the clinical study.
- AE monitoring (from the time the first dose of CO-1686 is administered through 28 days after the last dose, including study procedure-related AEs that occur after signing of the ICF and before administration of CO-1686)
- Blood sampling for biomarker/EGFR mutational testing and exploratory research that may lead to development of a plasma-based EGFR test. Detailed sample handling instructions are provided in the Laboratory Manual
- Optional participation in urine sampling for exploratory research. Instruct patients who have provided additional consent to collect first morning void on Day 1 of Cycles 1 – 6, and at the End of Treatment visit. Sample collection kits and written instructions will be provided. Patients will bring urine samples to the clinic for freezer storage and subsequent batch shipping. Sample handling instructions are provided in the Laboratory Manual.

9.3 Phase 1 – Dose Escalation Period

Before enrolling a patient into Phase 1, all eligibility criteria must be satisfied. Patients who qualify for the study will be enrolled into the first available cohort. Unless otherwise specified, all patients in Phase 1 will undergo the following procedures and assessments.

Patients will take CO-1686 daily, as directed. Oral CO-1686 should be taken with 8 oz. of water and with a meal, or within 30 minutes after a meal. Patients will record the dose and timing of administration of oral CO-1686 in their daily dosing diary.

9.3.1 *Day 1 of Cycle 1*

The following procedures will be completed before CO-1686 is administered:

- Physical examination
- Weight
- ECOG performance status
- Vital signs
- 12-lead ECG (in triplicate, 10-sec tracings > 2 min apart) prior to dosing
- Concomitant medications
- Hematology, reticulocyte count and serum chemistry.
- Predose blood sampling for biomarker/EGFR mutational testing and exploratory research
- Blood sample for CYP evaluation (optional sampling requires additional consent)
- Optional urine sampling prior to dosing. Instruct patients who have provided additional consent to collect first morning void in the sampling kit provided and bring the sample to the clinic for freezing and storage. (Cycles 1 – 6 only)
- AE monitoring including study procedure-related AEs that occur after signing of the ICF and before administration of CO-1686
- Quality of Life Questionnaires (EORTC QLQ Core 30 and Lung Cancer 13 and Dermatology Life Quality Index)
- PK blood and AAG serum samples (any time prior to dosing)
- 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.
- CO-1686 capsules or tablets will be dispensed to the patient

The following procedures will be performed over a 24-hour period after dosing. The frequency of the PK blood samples may require patients to stay overnight either at the clinic or in the vicinity.

- Postdose PK blood sampling collected at the time points (over 24 hours) specified in Section 9.8.3
- 12-lead ECG (in triplicate, 10-sec tracings > 2 min apart) as outlined in Table 13, following dosing with CO-1686
- AEs experienced by the patient since signing of informed consent will be documented
- Concomitant medications administered since dosing will be recorded
- Diary will be given to patient

9.3.2 *Days 8 and 15 of Cycle 1*

Patients will be instructed to refrain from taking their dose of oral CO-1686 at home because the dose will be taken during the clinic visit. The following procedures will be completed prior to administration of oral CO-1686 on Days 8 and 15 of Cycle 1.

- Physical examination
- Weight
- Vital signs
- Concomitant medications
- Hematology (including reticulocyte count) and serum chemistry
- AE monitoring
- PK blood sample and AAG serum samples (5 to 10 min prior to dosing) (Day 8 and Day 15).
- Predose blood sampling for biomarker/EGFR mutational testing and exploratory research.
- Collection and review of patient diary.
- 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. CO-1686 capsules or tablets will be dispensed to the patient.
- Day 15: 12-lead ECG (in triplicate, 10-sec tracings > 2 min apart) prior to dosing.
- Day 15: postdose 12-lead ECG (in triplicate, 10-sec tracings > 2 min apart), as outlined in Table 13, following dosing with CO-1686.
- Day 15: postdose PK blood sampling collected at the time points (over 24 hours) specified in Section 9.8.3. The frequency of the PK blood samples may require patients to stay overnight either at the clinic or in the vicinity.

9.3.3 *Phase 1: Food-effect PK Evaluation*

Patients participating in the food-effect PK evaluation only will take a **single** dose of CO-1686 1 week prior to the start of continuous daily dosing. These patients will undergo blood sampling for PK evaluation after dosing at the time points specified in Section 9.8.3. On Day 1 of Cycle 1, patients will consume a high-fat, high-calorie breakfast meal just prior to taking the dose of CO-1686, and will undergo blood sampling for PK evaluation at the time points specified in Section 9.8.1. The assessments and procedures are detailed below.

9.3.3.1 Day -7 Prior to Cycle 1

The patient will be instructed to arrive for their visit having fasted for at least 8 hours. The following procedures will be completed before receiving the dose of oral CO-1686. Any procedure, may be omitted if completed ≤3 days earlier during the screening period.

- Physical examination
- Weight

- ECOG performance status
- Vital signs
- Concomitant medications
- Hematology (including reticulocyte count) and serum chemistry
- AE monitoring
- PK blood sample (any time prior to dosing)
- A single dose of CO-1686 capsules or tablets administered to the patient, with 8 oz. (240 mL) of water. Patients must fast for at least 2 hours after dosing.

The following procedures will be performed over a 24-hour period after dosing. The frequency of the PK blood samples may require patients to stay overnight either at the clinic or in the vicinity.

- Postdose PK blood sampling collected at the time points specified in Section 9.8.3
- AEs experienced by the patient since dosing and/or before leaving the clinic will be documented
- Concomitant medications administered since dosing will be recorded

9.3.3.2 Day 1 of Cycle 1

The procedures described in Section 9.3.1, Day 1 of Cycle 1 should be followed with the exception of the fasting requirements. For patients participating in the food-effect PK evaluation, the following meal should be ingested following an overnight fast of at least 8 hours

- High-fat breakfast started (and completed within) 30 minutes prior to dosing with oral CO-1686

9.4 Phase 1 - Optional Treatment-Extension Period

Patients may participate in an optional Treatment-Extension Period that begins on Day 1 of Cycle 2, if the patient has tolerated the drug, has not progressed and if the treating physician believes it is in the patient's best interest to continue treatment. Patients will take CO-1686 at home at about the same time every day, except as noted below. Oral CO-1686 should be taken with 8 oz. of water. Patients will record the dose and timing of administration of oral CO-1686 in their daily dosing diary.

9.4.1 *Day 1 of Cycle 2 and Subsequent Cycles*

Patients will be instructed to refrain from taking their dose of oral CO-1686 at home on the day of their clinic visit because the dose will be taken during the clinic visit. On Day 1 of each cycle, patients participating in the optional Treatment-Extension Period will undergo the following procedures:

The following procedures are conducted before dosing with CO-1686:

- Physical examination

- Weight
- Vital signs and ECOG performance status
- 12-lead ECG (in triplicate, 10-sec tracings > 2 min apart) prior to dosing up to and including Cycle 12 for all patients. For patients who are ongoing at this time and for whom QT has been < 470 ms throughout the study, ECG monitoring may be subsequently evaluated every 3rd cycle thereafter (starting at Cycle 15).
- Hematology, including reticulocyte count, and fasting serum chemistry (for assessment of fasting glucose). Fasting glucose is required on Day 1 of every cycle. Hemoglobin A1c will be measured on Day 1 of every other cycle (Cycle 3, 5, 7, etc.).
- PK blood and AAG serum samples (any time prior to CO-1686 administration)
- Blood sampling for biomarker/EGFR mutational testing and exploratory research
- Optional urine sampling prior to dosing. Instruct patients who have provided additional consent to collect first morning void in the sampling kit provided and bring the sample to the clinic for freezing and storage. (Cycles 1 - 6 only)
- Concomitant medications and procedures
- AE monitoring
- Collection and review of patient diary
- Quality of Life Questionnaires (EORTC QLQ Core 30 and Lung Cancer 13 and Dermatology Life Quality Index) on Day 1 of Cycles 3, 5, and 7. After Cycle 7, questionnaires will be collected every 3 cycles (on Day 1 Cycles 10, 13, 16 etc.), and at End of Treatment.
- CO-1686 tablets will be dispensed 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.

The following procedures will be conducted after CO-1686 dosing:

- 12-lead ECG (in triplicate, 10-sec tracings > 2 min apart) 2 hours postdose up to and including Cycle 12 for all patients. For patients who are ongoing at this time and for whom QT has been < 470 ms throughout the study, ECG monitoring at this time point may be discontinued.
- Concomitant medications
- AE monitoring

The following procedure is conducted irrespective of dosing time:

Tumor scans (using the same methodology as was used at screening) at the end of Cycles 2, 4, and 6 (between Days 14 to 21), and every 3 cycles after Cycle 6 (between Days 14 to 21)

9.5 Phase 2

The assessments for Phase 2 Cohorts A to C will be identical.

Before enrolling a patient into Phase 2, all eligibility criteria must be satisfied. Except as noted, patients will take CO-1686 at home as directed, and record in the daily dosing diary.

9.5.1 *Day 1 of Cycle 1*

Procedures required on Day 1 of Cycle 1 may be omitted if completed ≤3 days earlier during the screening period. Patients should have been fasted for at least 8 hours prior to collection of sample for **fasting** serum chemistry.

The following procedures are conducted before dosing with CO-1686:

- Physical examination
- Weight
- ECOG performance status
- Vital signs
- 12-lead ECG (in triplicate, 10-sec tracings > 2 min apart) prior to dosing
- Concomitant medications and procedures
- Hematology (including reticulocytes) and **fasting** serum chemistry (for assessment of fasting glucose). C-peptide will be measured at Day 1 of every cycle.
- Blood sample for CYP evaluation (optional sampling requiring additional consent)
- Blood sampling for biomarker/EGFR mutational testing and exploratory research
- Phase 2 subset of patients taking part in dose level (500 mg BID and 625 mg BID) detailed PK profiling only: PK blood and AAG serum samples (any time prior to dosing). In addition 3 of the patients dosed at 625 mg BID will participate in CO-1686 metabolite profiling evaluation as described in Section 9.8.3.2.
- AE monitoring
- Quality of Life Questionnaires (EORTC QLQ Core 30 and Lung Cancer 13 and Dermatology Life Quality Index)
- Optional urine sampling prior to dosing. Instruct patients who have provided additional consent to collect first morning void in the sampling kit provided and bring the sample to the clinic for freezing and storage. (Cycles 1 to 6 only)
- Dispense tablets to 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.

The following procedures will be conducted after CO-1686 dosing:

- Phase 2 subset of patients taking part in dose level(500 mg BID and 625 mg BID) PK profiling only: PK blood sampling collected at the time points (over 24 hours) as specified in Section 9.8.3

- All patients: 12-lead ECG (in triplicate, 10-sec tracings > 2 min apart) 2 hours postdose
- Phase 2 subset of patients taking part in dose level PK profiling only- 12-lead ECGs (in triplicate, 10-sec tracings > 2 min apart), will be measured at the time points outlined in Table 13.

9.5.2 *Day 4 of Cycle 1 (±1 Day)*

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

- Fasting Glucose

9.5.3 *Day 8 of Cycle 1 (±1 Day)*

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

- Fasting Glucose

9.5.4 *Day 15 of Cycle 1 (±1 Day)*

Patients will be instructed to **refrain** from taking their dose of oral CO-1686 at home on the day of their clinic visit because the dose will be taken during the clinic visit. The following procedures will be completed:

The following procedures are conducted before dosing with CO-1686:

- Physical examination
- Weight
- Vital signs
- Concomitant medications
- Hematology, reticulocyte count and fasting serum chemistry (for assessment of fasting glucose).
- 12-lead ECG (in triplicate, 10-sec tracings > 2 min apart) prior to dosing
- Blood sampling for biomarker/EGFR mutational testing and exploratory research
- PK blood and AAG serum samples (5 to 10 min prior to dosing)
- AE monitoring
- Collection and review of patient diary
- Dispense capsules or tablets to 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.

The following procedures will be conducted after CO-1686 dosing:

- Phase 2 subset of patients taking part in dose level (500 mg BID and 625 mg BID) detailed PK profiling only: PK blood sampling collected at the time points (over 24 hours) as

specified in Section 9.8.3. In addition three of the patients dosed at 625 mg BID will participate in CO-1686 metabolite profiling evaluation as described in Section 9.8.3.2.

- All patients: 12-lead ECG (in triplicate, 10-sec tracings > 2 minutes apart) 2 hours postdose
- Phase 2 subset of patients taking part in dose level (500 mg BID and 625 mg BID) detailed PK profiling only - 12-lead ECGs (in triplicate, 10-sec tracings > 2 minutes apart), will be measured at the time points outlined in Table 13.

9.5.5 *Day 1 of Cycle 2 and Day 1 of Subsequent Cycles*

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:

The following procedures are conducted before dosing with CO-1686:

- Physical examination
- Weight
- ECOG performance status
- Vital signs
- 12-lead ECG (in triplicate, 10-sec tracings > 2 min apart) prior to dosing up to and including Cycle 12. 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.
- Concomitant medications and procedures
- Hematology (including reticulocyte count) and fasting serum chemistry (for assessment of fasting glucose). Fasting glucose is required on Day 1 of every cycle. Hemoglobin A1c will be measured on Day 1 of every other cycle (Cycle 3, 5, 7, etc.). C-peptide will be measured at Day 1 of every cycle.
- PK blood and AAG serum sampling (any time prior to dosing), up to and including Cycle 9 only
- Blood sampling for biomarker/EGFR mutational testing and exploratory research
- Optional urine sampling prior to dosing. Instruct patients who have provided additional consent to collect first morning void in the sampling kit provided and bring the sample to the clinic for freezing and storage. (Cycles 1 to 6 only)
- AE monitoring
- Collection and review of patient diary
- Quality of Life Questionnaires (EORTC QLQ Core 30 and Lung Cancer 13 and Dermatology Life Quality Index) on Day 1 of Cycles 3, 5, and 7. After Cycle 7, questionnaires will be collected every 3 cycles (on Day 1 Cycles 10, 13, 16, etc.), and at End of Treatment.
- Dispense capsules or tablets to 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.

The following procedures will be conducted after CO-1686 dosing:

- 12-lead ECG (in triplicate, 10-sec tracings > 2 minutes apart) 2 hours postdose up to and including Cycle 12. For patients who are ongoing at this time and for whom QT has been < 470 ms throughout the study, the 2 hour post dose ECG monitoring may be discontinued

The following procedure is conducted irrespective of dosing time:

- Tumor scans (using the same methodology as was used at screening) at the end of Cycles 2, 4, and 6 (between Days 14 and 21), and every 3 cycles after Cycle 6 (between Days 14 and 21)

9.5.6 *Cycle 2 Day 15 (±1 Day)*

The following procedures will be performed at C2 Day 15 (±1 day):

- Fasting Glucose

9.6 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 in both Phase 1 and 2 (Dose Escalation and Dose Expansion):

- Physical examination
- Weight
- ECOG performance status
- Vital signs
- Concomitant medications and procedures since last visit
- 12-lead ECG (in triplicate, 10-sec tracings > 2 min apart)
- Hematology, reticulocyte count, **fasting** serum chemistry (for assessment of fasting glucose)
- Serum pregnancy test for women of childbearing potential
- Tumor scans (using the same methodology as was used at screening), unless it has been < 2 weeks since last scan or disease progression was noted on the last scan
- Blood sampling for biomarker/EGFR mutational testing and exploratory research
- Optional tumor biopsy (requires additional consent)
- 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)
- Contraceptive counseling
- Quality of Life Questionnaires (EORTC QLQ Core 30 and Lung Cancer 13 and Dermatology Life Quality Index)
- Collection and review of patient diary

- Optional urine sampling. Instruct patients who have provided additional consent to collect first morning void on the day the End of Treatment visit is scheduled. Urine sample collection kits are provided and bring the sample to the clinic for freezing and storage.

9.7 Follow-up

The following data will be collected for all patients approximately every 2 months after treatment discontinuation until death, loss to follow-up, withdrawal of consent from study, or sponsor decision (Follow-up can be performed via the telephone):

- Subsequent treatments for NSCLC
- Overall survival information

9.8 Methods of Data Collection

9.8.1 *Safety Evaluations*

9.8.1.1 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, including study procedure-related AEs that occur after signing of the ICF and before administration of CO-1686. 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 4.0) and recorded on the eCRF.

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

9.8.1.2 Clinical Laboratory Investigations

Certified local laboratories will perform study-related clinical laboratory tests according to institutional procedures, and the results will be reviewed by the investigator. 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 three schedules of evaluation at screening, during treatment, and at the End of Treatment visit. Hematology results must be reviewed by the investigator prior to the start of treatment with oral CO-1686.

Patients known to require concomitant therapy with anticoagulant therapy such as warfarin should have 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, Cycle 1/Day 1, Cycle 1/Day 4, Cycle 1/Day 8, Cycle 1/Day 15, Cycle 2/Day 1, Cycle 2/Day 15, and Day 1 of every cycle thereafter and at End of Treatment visit, also if clinically indicated on study. Fasting glucose measure are part of the clinical chemistry panel (see below) on all Cycles Day 1 visits, and measured individually on Cycle 1/Day 4, Cycle 1/Day 8, Cycle 1/Day 15, and Cycle 2/Day 15.

Clinical Chemistry: Total protein, albumin, creatinine, BUN or urea, total bilirubin, alkaline phosphatase, ALT, AST, total cholesterol, fasting glucose, c-peptide, sodium, potassium, magnesium, chloride, CO2 (or bicarbonate), calcium, and phosphorus per the three schedules of evaluations at screening, during treatment, and at the End of Treatment visit. Serum levels of alpha-1 acid glycoprotein (AAG) will be determined on PK sampling days. Hemoglobin A1c will be measured at screening and on Day 1 of every other cycle (Cycle 3, 5, 7, etc.) while the patient is on study. C-peptide will be measured at screening, and Day 1 of every cycle.

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: Performed on women of childbearing potential ≤ 3 days before Day 1, Cycle 1, and at the End of Treatment visit. If the serum pregnancy test results are not available on Cycle 1/Day 1, a urine pregnancy test can be performed on Cycle 1/Day 1 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 oral 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.

9.8.1.3 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 each study visit including the End of Treatment visit.

9.8.1.4 12-Lead Electrocardiograms

Phase 1

For patients enrolled in Phase 1, serial 12-lead ECGs (10-sec ECG tracings collected in triplicate [> 2 min apart]) will be taken at the following time points and as clinically indicated:

- Screening: Anytime during the screening period
- Cycle 1, Day 1: predose and at multiple time points as outlined in Table 13, following dosing with CO-1686
- Cycle 1, Day 15: predose and at multiple time points as outlined in Table 13, following dosing with CO-1686
- All subsequent cycles: predose and at the estimated T_{max} (2 hours) postdose at Day 1 of each cycle
- End of Treatment: Any time after dosing has been discontinued, but within 28 days of last dose

Phase 2 – Subset of Patients Enrolled in Phase 2 and Participating in Detailed PK Profiling at 625 mg BID.

12-lead ECGs (10-sec ECG tracings collected in triplicate [> 2 minutes apart]) will be taken at the following time points and as clinically indicated:

- Screening: Anytime during the screening period
- Cycle 1, Day 1: predose**,** and at multiple time points as outlined in Table 13, following dosing with CO-1686
- Cycle 1, Day 15: predose, and at multiple time points as outlined in Table 13, following dosing with CO-1686
- All subsequent cycles: predose, and at the estimated T_{max} (2 hours) postdose at Day 1 of each cycle
- End of Treatment: Any time after dosing has been discontinued, but within 28 days of last dose

Phase 2 – All Other Patients

For patients enrolled in Phase 2 and not participating in full R2PD PK profiling, serial 12-lead ECGs (10-sec ECG tracings collected in triplicate [> 2 minutes apart]) will be performed at the following time points and as clinically indicated:

- Screening: within 28 days of first CO-1686 dose
- Cycle 1, Day 1: pre-dose and at the estimated T_{max} (2 hours) postdose
- Cycle 1, Day 15: pre-dose and at the estimated T_{max} (2 hours) postdose
- All subsequent cycles: predose and at the estimated T_{max} (2 hours) postdose at Day 1 of each cycle
- End of Treatment: Any time after dosing has been discontinued, but within 28 days of last dose

ECGs should be performed after the patient has been resting for at least 5 min. 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.

All Patients (Phase 1 and Phase 2)

Triplicate ECG monitoring will be conducted as outlined above up to and including Cycle 12. For patients who are ongoing at this time and for whom QT has been < 470 ms throughout the study, ECG monitoring may be subsequently reduced to predose evaluation and taken every 3rd cycle thereafter.

9.8.1.5 Body Weight and Height

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

9.8.1.6 Physical Examinations

Physical examinations will include an assessment of all the major body systems. Complete physical examinations will be performed at screening and at most study visits.

9.8.1.7 ECOG Performance Status

ECOG performance status (Appendix B) will be assessed at screening, on 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.

9.8.2 *Efficacy Evaluations*

9.8.2.1 Tumor Assessments

Tumor assessments will be performed at screening; at the end of Cycles 2, 4, and 6 (between Days 14 and 21); every 3 cycles after Cycle 6 (between Days 14 and 21); and at the End of Treatment visit. Tumor response will be interpreted using RECIST Version 1.1 (Appendix A).

If an initial CR or PR is noted at Cycle 7 or beyond, confirmatory scans must be performed 4 to 6 weeks 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 6 to 8 weeks.

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

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

Brain imaging (MRI/CT) is required at baseline. Patients with known brain metastases and/or brain lesions detected at baseline are required to repeat brain imaging as part of the follow-up tumor assessments. The same methods used to detect brain lesions at baseline are to be used to follow the same lesions throughout the clinical study.

9.8.3 *Pharmacokinetic Evaluations*

9.8.3.1 Phase 1

For patients in Phase 1, a serum AAG sample will be collected on each PK sampling day, and 2 mL venous blood samples for the PK analysis of oral CO-1686 will be drawn at the following time points:

- Cycle 1, Day 1: Prior to CO-1686 administration (any time prior to dosing), and at 15 (±2) minutes, 30 (±3) minutes, 1 hour. (±5 minutes), 1.5 hours (±5 minutes), 2.5 hours (±5 minutes), 4 hours (±15 minutes), 6 hours (±15 minutes), 8 hours (±15 minutes), 10 hours (±30 minutes), and 24 hours (±30 minutes) after dosing.
- Cycle 1, Day 8: At 5 to 10 minutes prior to CO-1686 administration.

- Cycle 1, Day 15***:*** At 5 to 10 minutes prior to CO-1686 administration, and at 15 (±2) minutes, 30 (±3) minutes, 1 hour (±5 minutes), 1.5 hours (±5 minutes), 2.5 hours (±5 minutes), 4 hours (±15 minutes), 6 hours (±15 minutes), 8 hours (±15 minutes), 10 hours (±30 minutes), and 24 hours (±30 minutes) after dosing.
- Cycle 2 and beyond, Day 1: Any time prior to CO-1686 administration.
- *On Cycle 1, Day 1 and Cycle 1, Day 15 a sample for AAG will be collected at the time of the pre-dose PK sample collection. On Cycle 1, Day 8 and Cycle 2 Day 1 and beyond, AAG will be collected at the time of PK sampling.*

Food-Effect PK Evaluation

- Day -7 prior to Cycle 1: Prior to CO-1686 administration (any time prior to dosing), and at 15 (±2) minutes, 30 (±3) minutes, 1 hour (±5 minutes), 1.5 hours (±5 minutes), 2.5 hours (±5 minutes), 4 hours (±15 minutes), 6 hours (±15 minutes), 8 hours (±15 minutes), 10 hours (±30 minutes), and 24 hours (±30 minutes) after dosing.

9.8.3.2 Phase 2 (Cohorts A to C)

For all patients in Phase 2, a serum AAG sample will be collected on each PK sampling day and a 2-mL venous blood samples for PK analysis of CO-1686 will be drawn at the following time points:

- Cycle 1 Day 15: 5 to 10 minutes prior to dosing with CO-1686
- Cycle 2 and beyond, Day 1 (up to and inclusive of Cycle 9, Day 1): any time prior to dosing with CO-1686

A sample for AAG will be collected at the time of PK sampling.

10 Patient Subset in Phase 2 at 500 mg BID and 625 mg BID.

For a subset of 10 patients in Phase 2 and at 500 mg BID and 625 mg BID, at a minimum, a serum AAG sample will be collected on each PK sampling day and 2-mL venous blood samples for the PK analysis of CO-1686 will be drawn at the following time points:

- Cycle 1, Day 1: Prior to CO-1686 administration (any time prior to dosing), and at 15 (±2) minutes, 30 (±3) minutes, 1 hour (±5 minutes), 1.5 hours (±5 minutes), 2.5 hours (±5 minutes), 4 hours (±15 minutes), 6 hours (±15 minutes), 8 hours (±15 minutes), 10 hours (±30 minutes), and 24 hours (±30 minutes) after dosing..
- Cycle 1, Day 15***:*** At 5–10 minutes prior to CO-1686 administration, and at 15 (±2) minutes, 30 (±3) minutes, 1 hour (±5 minutes), 1.5 hours (±5 minutes), 2.5 hours (±5 minutes), 4 hours (±15 minutes), 6 hours (±15 minutes), 8 hours (±15 minutes), 10 hours (±30 minutes), and 24 hours (±30 minutes) after dosing.
- Cycle 2 and beyond, Day 1 (up to and inclusive of Cycle 9, Day 1): any time prior to dosing with CO-1686

On Cycle 1, Day 1 and Cycle 1, Day 15 a sample for AAG will be collected at the time of the pre-dose PK sample collection. On Cycle 2 Day 1 and beyond, AAG will be collected at the time of PK sampling.

PK evaluation will be based on the determination of (not limited to) AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, $T_{1/2}$, and elimination rate constant (k_{el}), volume of distribution at steady state after non-IV administration (V_{ss}/F), and total plasma clearance after PO administration (Cl/F).

At least 3 of the full PK profile patients at the 625 mg BID dose level will participate in CO-1686 metabolite profiling at Cycle 1 Day 15.

- Cycle 1, Day 1: Prior to CO-1686 administration (any time prior to dosing).
    - ***Cycle 1 Day 1:*** An additional 2 mL sample will be collected prior to CO-1686 administration. This will serve as the baseline sample for subsequent profiling of CO-1686 circulating metabolites.
    - ***Cycle 1 Day 15:*** An additional 2 mL samples will be collected postdose at 30 (±3) minutes, 1.5 hours (±5 minutes), 4 hours (±15 minutes), 8 hours (±15 minutes), and 24 hours (±30 minutes) postdose.

Patients participating in Phase 2 full PK and metabolite assessments will be enrolled at a subset of sites.

For all Phase 1 and Phase 2 patients, the blood draw time relative to the last dosing time will be recorded at each PK sample occasion for each patient.

Central laboratories will be used for bioanalysis of oral CO-1686 and its metabolites in human plasma. In Phase 1 and Phase 2, a proportion of samples will be sent for routine analyses and a proportion of samples will be banked. Banked samples may subsequently be analyzed for exploratory PK/PD analyses.

Please refer to the laboratory manual for details on collection and processing of blood PK, metabolite and serum AAG samples.

9.8.4 *Baseline Tumor Biopsy and Matched Blood Sampling Requirements*

EGFR mutational status will be assessed in matching blood and tumor tissue 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. Biopsy of either primary or metastatic tumor tissue collected within 60 days of C1D1 is acceptable for use in screening only if: a) Biopsy is collected after signing ICF and all other screening activities occur within the 28-day screening window prior to C1D1, or b) Biopsy performed prior to patient signing informed consent is confirmed to have been done as routine standard of care and performed within 60 days of C1D1. 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 must be submitted to satisfy regulatory requirements for development and validation of the tissue-based companion diagnostic. Blocks will be returned upon request if required for legal or medical treatment purposes.

EGFR T790M eligibility testing for Phase 2 will be done by the sponsor's central laboratory. Matched blood sampling (up to 25 mL) should be collected prior to the biopsy procedure, if possible. Blood samples will be processed locally for plasma and stored frozen for subsequent batch shipping to the sponsor's lab.

- If a biopsy was performed within 60 days of Cycle 1, Day 1, 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. In this case, blood sampling should be taken at least 7 days AFTER the biopsy was performed.

When sufficient tissue is available from the baseline tumor biopsy, samples may be tested for molecular alterations that may modulate response or resistance to EGFR-targeted therapy.

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

9.8.5 *Pharmacodynamic Evaluations*

For all patients in Phase 1 and Phase 2 of the study, up to 25 mL of whole blood will be collected pre-dose on Days 1, 8 (Phase 1 only), 15 of Cycle 1, Day 1 of each treatment cycle, and at the End of Treatment visit for detection and quantification of mutant EGFR and further biomarker assessments in plasma. Samples may be used for the development of a blood-based diagnostic test.

Blood may also be used to test for biomarkers of response or resistance to EGFR-targeted therapy. Analysis may not be performed or only performed on a subset of patients if it becomes clear that the analysis will have limited scientific value (e.g., because of a very low titer of ctDNA in some patients, or if there are not enough serially collected samples from individual patients to allow for adequate biomarker evaluation).

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

9.8.6 *Optional Tumor Biopsy*

For patients who provide additional consent, an optional tumor biopsy may be collected at End of Treatment. This tissue may be analyzed for molecular alterations that modulate resistance to EGFR-targeted therapy.[7,19] Tissue preparation requirements are the same as listed in Section 9.8.4. Sample handling instructions will be provided in a separate laboratory manual.

9.8.7 *Pharmacogenetic Evaluations*

For patients who provide additional consent, genomic DNA will be extracted from a blood sample from each patient to detect genetic polymorphisms in CYP isoenzymes in order to explore the correlation between potential polymorphisms and drug exposure. For all patients in Phase 1 and Phase 2 of the study who provide additional consent, a single sample of up to 9 mL whole blood will be collected at Cycle 1, Day 1, to genotype the alleles of cytochrome P450 enzymes and drug transport proteins. Please see the Laboratory Manual for shipping and handling details.

9.8.8 *Optional Urine Sampling for Exploratory Research of Transrenal Nucleic Acids*

Sparse urine sampling will be collected from patients who choose to participate in this optional exploratory research. On Day 1 of Cycles 1 through 6, patients will collect approximately 100 mL of the first morning void using sampling kits provided and bring each sample to the clinic for freezing and storage. Frozen urine samples will be batched shipped to the sponsor's lab. Detailed sample handling instructions will be provided in the Laboratory Manual.

9.8.9 *Quality-of-Life Assessments*

Quality of life will be measured using the EORTC QLQ Core 30 and Lung Cancer 13 and the Dermatology Life Quality Index (DLQI), which will be administered at baseline, every two cycles through Cycle 6 and then every 3 cycles thereafter.

9.8.10 *Patient Diary Cards*

Patient diary cards will be provided to patients. Patient will use diary cards 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 non-leading question (e.g., "Have you experienced any new or changed symptoms since we last asked/since your last visit?"). AEs will be reported on the AE eCRF. Symptoms reported spontaneously by the patient during the physical examination will also be documented on the AE eCRF (not on the physical examination eCRF, which is reserved for physical signs or findings).

10.2 Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that occurs at any dose (from the time the first dose of CO-1686 is administered through 28 days after the last dose, including study procedure-related AEs that occur after signing of the ICF and before administration 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 oral CO-1686 will 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 (e.g., respite care)
- Overdose of either Clovis study drug or concomitant medication unless the event meets SAE criteria (e.g., hospitalization). However, the event should still be captured as a non-serious AE on the appropriate eCRF page
- Events of progression of the patient's underlying cancer as well as events clearly related to progression of the patient's cancer (signs and symptoms of progression) should not be reported as a serious adverse event unless the outcome is fatal during the study or within the safety reporting period. If the event has a fatal outcome during the study or within the safety reporting period, then the event of Progression of Disease must be recorded as an AE and as an SAE with CTC 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 serious adverse events

10.4 Clinical Laboratory Assessments and Other Abnormal 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

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. **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, including study procedure-related AEs that occur after signing of the ICF and before administration of CO-1686 will be recorded on the AE 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 into a final diagnosis. For example, fever, cough, and shortness of breath may be reported as pneumonia, 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's SAE designee.

10.6.1 *Intensity of Adverse Events*

The severity of the AE will be graded according to the NCI CTCAE Version 4.0 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 *Relationship of Adverse Events to Investigational Medicinal Products*

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

Not Related

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

- An alternative explanation is likely but not clearly identifiable

Related

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

10.6.3 *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. Any SAEs must be followed until resolution or stabilization.

10.8 Regulatory Aspects of Adverse Event Reporting

All SAEs, regardless of relationship to study drug, must be reported to the sponsor or 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.

The sponsor or its designee is responsible for submitting reports of AEs associated with the use of the drug that are both serious and unexpected to the 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 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 Institutional Review Board (IRB) or Independent Ethics Committee (IEC). In accordance with the European Commission Clinical Trials Directive (2001/20/EC), the sponsor or its designee will notify the relevant ethics committees in concerned member states of applicable suspected unexpected serious adverse reactions (SUSARs) as individual notifications or through periodic line listings.

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

11 STATISTICAL METHODS

11.1 Populations

The following analysis populations are defined for the study:

PK-evaluable Population—all patients who received at least one dose of CO-1686 and have adequate PK assessments drawn for determination of the PK profile. Adequacy will be determined on a case-by-case basis and will be assessed prior to analysis of the blood samples.

Food-effect PK Population—all patients who enrolled into a food-effect PK evaluation cohort who received CO-1686 on both Day -7 and Day 1, complied with the fed and fasted requirements, and have sufficient PK data for a comparison to be made between the fasted and fed state.

ECG/PK Comparison-Evaluable Population—all patients in Phase 1 and Phase 2 who have received CO-1686 and have had adequate PK and ECG assessments performed for determination of the ECG effects and the relationship between PK and ECG.

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

DLT-evaluable Population—all patients enrolled into Phase 1 of the study who received at least 80% of scheduled doses of CO-1686 and completed Cycle 1 of treatment, or who experienced a DLT in Cycle 1.

Tumor-evaluable Population—all patients who received at least one dose of CO-1686, have measurable tumor lesions at baseline, and have at least one post-baseline disease assessment.

11.2 Statistical Methods

11.2.1 *General Considerations*

Quantitative variables will be summarized using descriptive statistics (N, mean, standard deviation, median, minimum, and maximum) and/or frequency and percentages for medically relevant categories. Categorical variables will be presented using frequencies and percentages. The Kaplan-Meier methodology will be used to summarize time-to-event variables. If estimable, the 25th, 50th (median), and 75th percentiles will be presented. The number of patients with events and the number of censored patients will also be presented.

Individual patient data listings will be provided to support summary tables. 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, Version 9.1 or higher.

11.2.2 *Patient Disposition*

Separately for Phase 1 and Phase 2 of the study, 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*

Separately for Phase 1 and Phase 2 of the study, baseline characteristics and demographic data will be summarized for the safety population.

11.2.4 *Efficacy Analyses*

11.2.4.1 Phase 1

Overall Response Rate - Secondary Endpoint

A secondary endpoint in Phase 1 of the study (overall response rate) is the best overall response recorded from the start of the treatment until disease progression or recurrence. The overall response rate will be summarized for the tumor-evaluable population enrolled in Phase 1 with frequencies and percentages.

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

Duration of Response - Secondary Endpoint

Duration of response for complete response (CR) and partial response (PR) will be measured from the date that any of these best responses is first recorded until the first date that progressive disease is objectively documented. Duration of response will be summarized using descriptive statistics (N, mean, standard deviation, median, minimum, and maximum) as well as categorically.

11.2.4.2 Phase 2 (Cohorts A to C)

The efficacy results from Phase 1 and Phase 2 may be presented together for certain dose groups of interest.

Objective Response Rate (ORR) - Primary Endpoint

A primary endpoint in Phase 2 of the study (objective response rate) is the best response recorded from the start of the treatment until disease progression or recurrence. The frequency and percentages of patients with a best response of CR, PR, stable disease (SD), or progressive disease (PD) will be summarized for the tumor-evaluable and safety populations enrolled in Phase 2. The response rate (CR+PR) will also be presented with frequencies and percentages.

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

The ORR will be evaluated by the investigator with the primary analysis based on investigator assessment.

Duration of Response - Primary Endpoint

Duration of response 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. Duration of response will be summarized using descriptive statistics (N, mean, standard deviation, median, minimum, and maximum) as well as categorically.

The duration of response will be evaluated by the investigator with the primary analysis based on investigator assessment.

Objective Response Rate (ORR) by IRR- Secondary Endpoint

A secondary endpoint in Phase 2 of the study (objective response rate) is the best response recorded from the start of the treatment until disease progression or recurrence. The frequency and percentages of patients with a best response of CR, PR, SD, or PD will be summarized for the tumor-evaluable and safety populations enrolled in Phase 2. The response rate (CR+PR) will also be presented with frequencies and percentages.

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

The ORR will be evaluated by the central independent radiology review (IRR).

Duration of Response by IRR – Secondary Endpoint

Duration of response 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. Duration of response will be summarized using descriptive statistics (N, mean, standard deviation, median, minimum, and maximum) as well as categorically.

The duration of response will be evaluated by the IRR with the analysis based on independent assessment.

Overall Survival (OS) - Secondary Endpoint

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.

Disease Control Rate (DCR) - Secondary Endpoint

The DCR is the percentage of patients with a best response of CR, PR, or SD for at least 12 weeks.

The DCR will be evaluated by the investigator and the IRR.

Progression-free Survival (PFS) - Secondary Endpoint

Progression-free survival will be calculated as the number of days from the date of the first dose of CO-1686 to the date of disease progression or death due to any cause + 1. Patients without a documented event of disease 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. Any valid tumor measurements are considered adequate for efficacy assessments. Patients with measurable disease at baseline will have disease progression determined by RECIST Version 1.1 criteria.

The Kaplan-Meier methodology will be used to summarize progression-free survival. The 25th, 50th (median), and 75th percentiles will be presented.

PFS will be evaluated by the investigator and by IRR.

11.2.5 *Pharmacokinetic Analyses – Secondary Endpoint*

As a primary endpoint in Phase 1 and a secondary endpoint in Phase 2 of the study, PK parameters will be determined using noncompartmental methods. AUC from Time 0 to the last

observation will be calculated using the trapezoid rule. The k_{el} will be calculated using log-linear regression on the terminal part of the concentration time curve. The terminal half-life and the AUC from the last observation to infinity will be calculated from the estimated k_{el}. Other parameters to be determined are C_{max}, T_{max}, V_{ss}/F, and Cl/F.

As a secondary endpoint in Phase 1, the effect of food on PK parameters including, but not limited to, C_{max} and AUC, will be compared using analysis of variance (ANOVA) techniques.

As a secondary endpoint in Phase 2, additional plasma samples will be collected on Day 15 from a minimum of three patients enrolled at the RP2D. Individual pooled plasma samples, one from each of these patients, will be prepared using the method proposed by Hamilton.[24] The pooled plasma samples will be further processed before being analyzed by high-performance liquid chromatography coupled in-line with ultraviolet spectrophotometric and tandem mass spectrometric detection (HPLC-UV-MS/MS).

A specific population PK data analysis plan will be developed and will outline the detailed approach to data handling, model development and diagnostics, individual model parameter estimation, exploration of covariate effects, and final model evaluation techniques.

11.2.6 *Patient Reported Outcomes – Secondary Endpoint*

Patient reported outcome questionnaires, the EORTC QLQ C30 and LC13 and the Dermatology Life Quality Index will be summarized with descriptive statistics on observed data for all three PRO instruments and their subscales. Specifically, the domain and item scores from the EORTC-QLQ-C30 (global health status; physical, role, emotional, cognitive, and social functioning; fatigue, nausea and vomiting, and pain symptoms; dyspnea; insomnia; appetite loss; constipation; diarrhea; and financial difficulties), from the lung cancer module (dyspnea**,** coughing, hemoptysis, sore mouth, dysphagia, peripheral neuropathy, alopecia, pain in chest, pain in arm or shoulder, and pain in other parts) and from the DLQI (DLQI total score, daily activities, leisure, personal relationships, symptoms and feelings, treatment, and work/school) will be summarized using descriptive statistics (i.e., N, mean, StDev, median, Q1, Q3, min, and max) at each scheduled assessment point by phase and overall. Additionally, change from baseline in the domain and item scores at the time of each assessment will be summarized.

Mean changes from baseline (including standard deviation bars) in EORTC-QLQ-C30 lung cancer module symptom scores and DLQI domain scores will be plotted at each assessment point. At each assessment point on the x axis the number of patients completing the assessment for each treatment group should be listed. The y axis should encompass only the range of values reported by patients in the study (as opposed to the full range of the scale).

Additional details on the analysis of the patient reported outcome data will be provided in the statistical analysis plan.

11.2.7 *Relationship Between PK and QTc – Secondary Endpoint*

In Phase 1 patients and in a subset of Phase 2 patients participating in full PK profiling, an endpoint of the study will be to examine the relationship between the concentration of oral CO-1686 (PK) and potential changes in QTc. A linear and nonlinear mixed effect modeling approach will be used to quantify the relationship between the plasma concentration and the ΔQTc baseline-adjusted difference in QTc interval. Plots of the mean QT/QTc versus drug concentrations and a concentration-QT variables correlation will be explored.

11.2.8 *Time to Treatment Failure - Exploratory Endpoint*

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.

The subgroup of patients that continue receiving study drug past an event of disease progression will be summarized separately.

11.2.9 *Concordance of T790M in Tumor versus Blood – Exploratory Endpoint*

An exploratory pharmacodynamic endpoint is the detection and quantification of mutant EGFR cell-free DNA in blood collected at baseline and with every tumor assessment. The presence of the T790M mutation at baseline and subsequent time points will be presented both with frequencies and percentages. In addition, the relationship between T790M detected in tumor compared with that detected in blood, and urine where applicable, will be explored. This will involve determining the sensitivity, specificity, positive and negative predictive values with 95% confidence intervals (CIs) of blood with respect to tumor assuming that EGFR mutational status in tumor is a true reflection of tumor biology. Blood collected at these time points may also be assessed for cell-free DNA related to biomarkers of response or resistance to EGFR-targeted therapy.

11.2.10 *Safety Analyses*

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

11.2.10.1 Extent of Exposure

The following will be summarized by dose group using descriptive statistics:

- Number of patients dosed in Phase 1 (Dose-escalation Period and Treatment-extension Period and RP2D Exploratory cohort), and in Phase 2
- Number of patients at each dose group, average dose amount, total cumulative dose (Phase 1 and 2)
- Number of cycles initiated (Phase 1 and 2)
- Number of dose reductions/delays (Phase 1 and 2)
- Number of dose interruptions (Phase 1 and 2)
- Duration of exposure (Phase 1 and 2)

The number of patients at each dose group or study phase will be summarized with frequencies and percentages; the average dose, total cumulative dose, and duration of exposure will be summarized with descriptive statistics and frequency counts for relevant categories. The number of cycles initiated will be investigated by summarizing the number of cycles started by each patient in each period. The number of patients with at least one dose reduction/delay or interruption will be summarized with frequencies and percentages.

11.2.10.2 Adverse Events

AE coding will be performed using the Medical Dictionary for Drug Regulatory Activities, Version 13.0 or greater. The severity of the toxicities will be graded according to the NCI

CTCAE Version 4.0 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 system organ class and preferred term will be presented by dose group. Multiple instances of the treatment-emergent AEs in each system organ class and multiple occurrences of the same preferred term are counted only once per patient. The number and percentage of patients with at least one treatment-emergent AE will also be summarized by dose group.

Separate tables will present the following by dose group and study phase:

- All treatment-emergent AEs
- Treatment-emergent AEs by CTCAE grade
- Grade 3 or greater treatment-emergent AEs
- Treatment-related, treatment-emergent AEs
- Dose-limiting toxicity AEs
- Serious treatment-emergent AEs
- Serious treatment-related AEs
- Treatment-emergent AEs with an outcome of death
- Treatment-emergent AEs leading to discontinuation of oral CO-1686
- Treatment-emergent AEs resulting in interruption or reduction/delay of CO-1686

The incidence of treatment-emergent AEs will be summarized by relationship to oral CO-1686 using "treatment-related" and "not treatment-related" categories. The category of treatment-related is defined as a relationship of Possible/Probable, Definite, or Missing. 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 one treatment-emergent AE of the given grade will be summarized.

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

11.2.10.3 Clinical Laboratory Evaluations

Clinical laboratory evaluations include the continuous variables for hematology, serum chemistry, and urinalysis. Laboratory values will be presented in Systeme International units. The baseline laboratory value will be defined as the last value prior to or on the day of the first dose of oral CO-1686. The on-treatment period will be defined as the day after the first dose of oral 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 by dose group and study phase. Summaries using descriptive statistics of the change from baseline to the maximum, minimum, and last value during the on-treatment period will also be given by dose group and study phase. Supporting laboratory data including normal ranges and abnormal laboratory flags will be provided using by-patient listings. Separate listings will be produced for clinically significant laboratory abnormalities (i.e., those that meet Grade 3 or 4 criteria according to CTCAE Version 4.0) by dose group.

11.2.10.4 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 by dose group and study phase. Summaries using descriptive statistics of the change from baseline to the maximum, minimum, and last value during the on-treatment period will also be given by dose group.

11.2.10.5 12-Lead Electrocardiograms

ECG intervals will be stratified into categories indicative of potential clinical significance. Each patient's maximum QT and QTc intervals from the pretreatment visit and treatment period visits will be classified as ≤450 msec, > 450 to ≤480 msec, > 480 to ≤500 msec, and > 500 msec. For each patient's maximum change from the pretreatment ECG visit for QT and QTc, intervals will be classified into < 30 msec, ≥30 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/QTc over time for Day 1 and Day 15 of Cycle 1 and End of Treatment/pretreatment ECG day measurements will be provided.

11.2.10.6 Other Safety Measurements

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

11.3 Interim Analyses

Separately within each new dose level in Cohorts A and B (Cohort A and B - 500 mg BID and 625 mg BID), the ORR will be evaluated in the first 12 patients. Within Cohort C, the ORR will be evaluated separately for patients from the 2 patient populations represented by Cohorts A and

B. If zero responses are observed in the first 12 patients within each dose level (Cohorts A and B) or patient population (Cohort C) are observed, then the respective level or population may be discontinued due to a lack of efficacy. If zero PR or CR responses are observed in 12 patients then there is a high probability that the true objective response rate is less than 20%. In addition to the futility analyses within each cohort, formal safety data reviews will occur following the enrollment of every 50 patients and approximately every 6 months once enrollment is completed and as long as patients remain on treatment. The review committee will include external experts and sponsor personnel. The external experts will include, but not be limited to, the coordinating PIs of the study. The sponsor's reviewers will include the Medical Monitor, Chief Medical Officer, and Biostatistician. The protocol will be amended as appropriate to incorporate additional patient safety monitoring if new safety signals are noted at any review.

11.4 Sample Size Considerations

Amendment 6 allowed for at least approximately 380 efficacy-evaluable patients to be enrolled into Cohorts A and B for the Phase 2 portion of the study (up to approximately 75 patients per dose level 625 mg BID and 500 mg BID, up to approximately 40 patients at 750 mg BID). The patients eligible for Cohort A and B under this amendment will be assigned to receive either 500 mg BID or 625 mg BID by the sponsor, so that Cohort B will contain up to approximately 150 patients and Cohort A may contain up to approximately 275 patients. Amendment 7 allowed the later-line patient population in Cohort A (more prevalent population) to continue enrollment as long as the earlier line patient population, Cohort B, is open for enrollment. Based on current enrollment rates, the size of Cohort A will increase from 150 patients to approximately 275 patients.

Up to approximately 100 efficacy-evaluable patients will be enrolled into Cohort C in the Phase 2 portion of the study.

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 5.1.4.
- 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
- Non-compliance as described in Section 7.7
- A positive pregnancy test at any time during the study

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 oral 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. Patients will be followed for 28 days after the last dose of CO-1686 for safety; those with ongoing SAEs will be followed until either resolution or stabilization has been determined.

12.2 Study Stopping Rules

In the event a DLT rate of greater than 33% is observed at the starting dose (150 mg) and schedule (daily for 21 days), then other dosing schedules may be explored.

13 STUDY ADMINISTRATION

13.1 Regulatory and Ethical Considerations

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

13.1.1 *Regulatory Authority Approvals*

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

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

US-generated data will be handled in accordance with the Health Information Portability and Accountability Act (HIPAA). The trial will be registered 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.

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

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

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

The IEC/IRB must be informed by the principal investigator of all subsequent study protocol amendments and of SAEs or suspected unexpected adverse reactions (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 the sponsor, 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 informed consent form, 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 informed consent forms 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 informed consent form, 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 informed consent form consistent with the study protocol version used and approved by the relevant IEC/IRB. The informed consent form 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 informed consent form. A copy of the signed informed consent form 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 the sponsor may also contact and visit the investigators and monitor data during the study.

13.5 Case Report Form

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

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

For each patient enrolled, an eCRF must be completed, reviewed, signed, and dated by the principal investigator or co-investigator within a reasonable time period (< 3 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, the sponsor and the investigator will assure that adequate consideration is given to the protection of the patients' interests.

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

The entire study will be stopped if:

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

- The sponsor discontinues the development of oral CO-1686.

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

13.7 Modification of the Study Protocol

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

13.8 Retention of Study Documents

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

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

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

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

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

13.9 Clinical Study Report

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

13.10 Study Publication

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

13.11 Quality Assurance Audits

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

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15 APPENDICES

Appendix A. Response Evaluation Criteria in Solid Tumors Criteria

Appendix B. Eastern Cooperative Oncology Group Performance Status Scale

Appendix C. Bayesian Dose Escalation Design for CO-1686-008

Appendix D. Study CO-1686-008 Extension Phase

Appendix A
Response Evaluation Criteria in Solid Tumors Criteria

The RECIST guidelines (Version 1.1) are described in Eisenhauer (2009)[25] 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 Nontarget Lesions

Complete Response	Disappearance of all nontarget lesions and normalization of tumor marker level. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
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; e.g., if only 2 of 3 baseline target lesions are assessed and result in a > 20% increase in the sum, then the patient would be assessed as a PD regardless of the missing lesion.

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

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

Confirmatory Measurement/Duration of Response

Confirmation

CT scans are required within 7 days prior to the start of Cycles 3, 5, and 7, and then within 7 days prior to the start of every third cycle of treatment thereafter, beginning with Cycle 10. If an initial CR or PR is noted at Cycle 7 or beyond, confirmatory scans must be performed 4 to 6 weeks 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 6 to 8 weeks.

Duration of Overall Response

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

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

Duration of Stable Disease

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

Appendix B
Eastern Cooperative Oncology Group Performance Status Scale

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

Appendix C
Bayesian Dose Escalation Design for CO-1686-008

1.0 Introduction

This appendix provides a description of the trial design along with details of the statistical model and simulation results.

Dose escalation will be conducted according to a continual reassessment method (CRM) based on a statistical model for dose limiting toxicities (DLTs). The treatment cycle length is 21 days, with DLT evaluated during the first cycle.

2.0 Endpoints

The primary safety endpoint is the rate of dose-limiting toxicity. The MTD is defined as the highest dose that has an estimated DLT rate less than 33%.

3.0 Dose Range

In the model, dose d refers to the total daily dose administered. The starting dose for the study will be d = 1000 mg (500 mg administered twice daily). The anticipated maximum daily dose will be d = 2250 mg and the anticipated minimum will be 500 mg.

4.0 Statistical Model

Dose escalation will be conducted according to a CRM algorithm. We construct a statistical model to describe the relationship between dose and DLT rate.

We let Y be an indicator of DLT (1 = DLT and 0 = no DLT) and define θ_d to be the probability of DLT at dose d. We model the log-odds of θ_d with a two-parameter model:

$$\log\left(\frac{\theta_d}{1-\theta_d}\right) = \alpha + \beta\left(\frac{d}{100}\right)$$

where d is the magnitude of dose (mg).

We create a prior distribution for the parameters capturing the correlation between the parameters that is expected. In order to accomplish this we create independent priors and use pseudo-prior observations in the likelihood function to create prior distributions that are more appropriate. We place the following independent prior distributions on the parameters:

$$\alpha \sim N(-4, 2^2)$$

$$\beta \sim N(0.1, 0.25^2).$$

We use "pseudo-prior" weighting to impose the appropriate weight in the prior distribution. We assume ½ an observation on the highest and lowest dose, with 0 DLTs on the lowest dose and ½ DLT on the highest dose.

After each patient is treated and assessed for DLT, the distributions of these parameters are updated and a next dose level is suggested based on the posterior probability of the DLT rate at each dose.

Additionally, we define a dose as unsafe if there is more than 50% probability that the DLT rate exceeds 33%:

$$\Pr(\theta_d > 33\%) > 50\%.$$

Patients cannot be assigned to a dose that is unsafe by this definition.

5.0 Adaptive Design

In addition to the CRM-modeling, there are additional rules governing entry into the study and assignment of dose level.

5.1 Entry into the Study

There is open enrollment into the study with the following restrictions:

- There can be no more than 6 patients with unknown DLT information at any time. We refer to the number of subjects waiting for DLT information as the "queue."
- Complete DLT information is required for at least 3 patients at a dose before escalation to a higher dose.

5.2 Assignment of Dose Level

The CRM will be used to assign patients to doses. However, the maximum increment from one dose to the next is anticipated to be 250 mg total daily dose. The design is structured to assign one of the following 7 doses: 750 mg, 1000 mg, 1250 mg, 1500 mg, 1750 mg, 2000 mg or 2250 mg.

5.3 Safety Monitoring

If no doses are safe, that is, $\Pr(\theta_d > 33\%) > 50\%$ for all d, then the trial may de-escalate to 750 mg or 500 mg. If 500 mg is also unsafe, then the study will pause enrollment for further evaluation.

5.4 Success in Identifying the MTD

Dose escalation is considered successful – and an MTD identified – when at least 10 patients have been enrolled at the estimated MTD. Once the MTD has been identified, additional patients will be enrolled at that dose (if R2PD is the same as the MTD), to approximately 40 patients eligible for Phase 2 Cohort A and up to approximately 40 patients eligible for Phase 2 Cohort B.

6.0 Example Dose Escalation

In this section, we present selected snapshots from an example trial to illustrate the dose escalation process.

The trial begins by allocating subjects to a total daily dose of 1000 mg. The first opportunity for escalation will be after DLT information is available from 3 patients at this dose, but we allow additional patients to enroll while waiting for these subjects to reach the end of Cycle 1. The total queue of incomplete data may never exceed 6 patients.

Table 4.1 shows a snapshot of the data when a 7th patient becomes available to enter the trial. The row Pr(DLT) gives the model-estimated DLT rate for each dose and Pr(Safe) is the probability that the DLT rate is below 33%. As discussed in Section 5.3, no patients may be assigned to a dose where this probability is below 50%.

Table 4.1

	500	750	1000	1250	1500	1750	2000	2250
Enrolled	--	--	6	--	--	--	--	--
Complete	--	--	3	--	--	--	--	--
DLT	--	--	1	--	--	--	--	--
Pr(DLT)	0.131	0.206	0.316	0.443	0.561	0.656	0.727	0.780
Pr(Safe)	0.923	0.807	0.584	0.373	0.245	0.170	0.127	0.103

At this time, 6 patients are enrolled at 1000 mg, three of which have completed Cycle 1, and one DLT. Thus, the queue is 3 subjects with unknown information. The next highest dose of 1250 mg is not considered safe at this time, so enrollment continues at the 1000 mg dose.

When the 10th patient arrives, complete information is available from 5 patients at 1000 mg, as shown in Table 4.2. No additional DLTs were observed, and the estimated probabilities have decreased across all doses. The next highest dose is considered safe with Pr($\theta < 33\%$) = 0.558. Thus, the 1250 mg dose is opened for enrollment.

Table 4.2

	500	750	1000	1250	1500	1750	2000	2250
Enrolled	--	--	9	--	--	--	--	--
Complete	--	--	5	--	--	--	--	--
DLT	--	--	1	--	--	--	--	--
Pr(DLT)	0.092	0.140	0.220	0.328	0.444	0.549	0.634	0.699
Pr(Safe)	0.973	0.934	0.786	0.558	0.381	0.269	0.201	0.162

Table 4.3 shows the updated model after 3 patients have completed the DLT period at the 1250 mg dose. One DLT was observed in this cohort. The model estimates that the next highest dose is unsafe, so enrollment continues at the current dose.

Table 4.3

	500	750	1000	1250	1500	1750	2000	2250
Enrolled	--	--	9	8	--	--	--	--
Complete	--	--	9	3	--	--	--	--
DLT	--	--	1	1	--	--	--	--
Pr(DLT)	0.065	0.099	0.159	0.253	0.372	0.493	0.596	0.676
Pr(Safe)	0.995	0.992	0.953	0.736	0.464	0.295	0.203	0.153

The next patient completes Cycle 1 without DLT. We update the model to incorporate the accumulating data (Table 4.4). The 1500 mg dose is considered safe and will now be opened for enrollment.

Table 4.4

	500	750	1000	1250	1500	1750	2000	2250
Enrolled	--	--	9	9	--	--	--	--
Complete	--	--	9	4	--	--	--	--
DLT	--	--	1	1	--	--	--	--
Pr(DLT)	0.063	0.093	0.144	0.227	0.335	0.450	0.552	0.634
Pr(Safe)	0.995	0.994	0.969	0.803	0.538	0.355	0.251	0.193

The next opportunity for escalation occurs after 3 subjects complete the DLT period at 1500 mg. There are actually 4 evaluable patients at that time, and no DLT (Table 4.5). Additionally, all patients at the 1250 mg dose have now completed the DLT period. Dose 1750 mg is considered safe, and the next patient is assigned to 1750 mg.

Table 4.5

	500	750	1000	1250	1500	1750	2000	2250
Enrolled	--	--	9	9	8	--	--	--
Complete	--	--	9	9	4	--	--	--
DLT	--	--	1	2	0	--	--	--
Pr(DLT)	0.063	0.080	0.108	0.152	0.216	0.297	0.385	0.467
Pr(Safe)	0.995	0.997	0.997	0.979	0.842	0.619	0.543	0.349

Table 4.6 shows the data and model estimates after 4 patients have complete information at 1750 mg. The next highest dose is considered safe, so new patients will be allocated to 2000 mg.

Table 4.6

	500	750	1000	1250	1500	1750	2000	2250
Enrolled	--	--	9	9	8	7	--	--
Complete	--	--	9	9	8	4	--	--
DLT	--	--	1	2	0	1	--	--
Pr(DLT)	0.065	0.077	0.096	0.125	0.168	0.225	0.295	0.369
Pr(Safe)	0.993	0.997	0.999	0.997	0.968	0.820	0.622	0.215

After 2 patients have been enrolled at 2000 mg, all remaining patients at 1750 mg have complete data. We observed a total of 4 DLTs out of 7 patients at that dose. In reaction to this accumulating data, the model now believes that 1500 mg is the highest dose that is safe.

Table 4.7

	500	750	1000	1250	1500	1750	2000	2250
Enrolled	--	--	9	9	8	7	2	--
Complete	--	--	9	9	8	7	0	--
DLT	--	--	1	2	0	4	--	--
Pr(DLT)	0.049	0.073	0.110	0.171	0.261	0.380	0.508	0.624
Pr(Safe)	0.998	0.999	0.998	0.987	0.805	0.363	0.151	0.081

When 10 patients are enrolled at 1500 mg, escalation stops. The final follow-up data are shown in Table 4.8.

Table 4.8

	500	750	1000	1250	1500	1750	2000	2250
Enrolled	--	--	9	9	10	7	2	--
Complete	--	--	9	9	10	7	2	--
DLT	--	--	1	2	1	4	1	--
Pr(DLT)	0.051	0.076	0.116	0.180	0.275	0.398	0.530	0.648
Pr(Safe)	0.999	0.998	0.997	0.983	0.771	0.283	0.093	0.043

7.0 Simulations and Operating Characteristics

In order to evaluate the performance of the dose escalation design, we simulated the study under different dose-toxicity scenarios.

7.1 Dose-toxicity Profiles

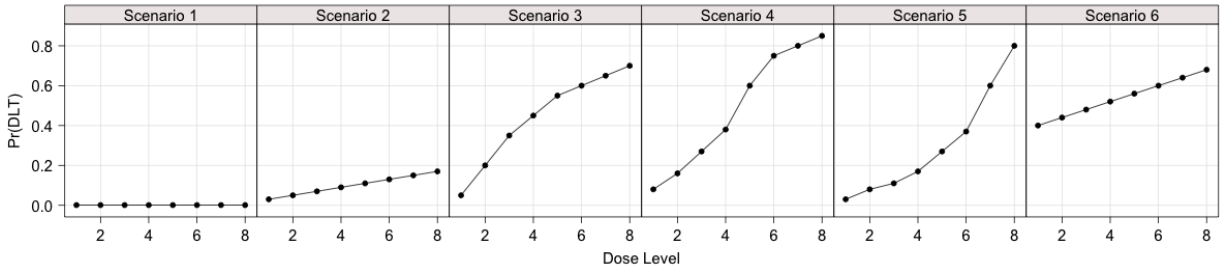
We considered six scenarios for the underlying DLT rate on each dose. Scenario 1 is a flat dose-toxicity curve in which all doses are safe. In Scenario 2, the curve is increasing, but all doses are below the target toxicity level. Scenarios 3 through 5 assume that the MTD is at the low, middle, or high end of the dose range. In Scenario 6, all doses are unsafe.

These profiles are shown in Table 5.1 and are displayed graphically in Figure 5.1. The true MTD appears as red italic font in the table.

Table 5.1 Dose-toxicity Profiles

Scenario	DLT Rate							
	500	**750**	**1000**	**1250**	**1500**	**1750**	**2000**	**2250**
1	0.001	0.001	0.001	0.001	0.001	0.001	0.001	***0.001***
2	0.030	0.050	0.070	0.090	0.110	0.130	0.150	***0.170***
3	0.050	***0.200***	0.350	0.450	0.550	0.600	0.650	0.700
4	0.080	0.160	***0.270***	0.380	0.600	0.750	0.800	0.850
5	0.030	0.080	0.110	0.170	***0.270***	0.370	0.600	0.800
6	0.400	0.440	0.480	0.520	0.560	0.600	0.640	0.680

Figure 5.1 Dose-toxicity Profiles



7.2 Accrual

We simulated patient accrual to the trial from a Poisson process. We assumed that accrual will be at the rate of 6 patients per month.

7.3 Operating Characteristics

We simulated the six scenarios for 1000 trials per scenario.

Table 5.2 shows the proportion of simulated trials for which each dose was selected as the MTD after all subjects had complete DLT information, and the average number of patients treated at each dose. The true MTD is shown in bold italics. The last column shows the proportion of trials for which no MTD was identified, due to toxicity.

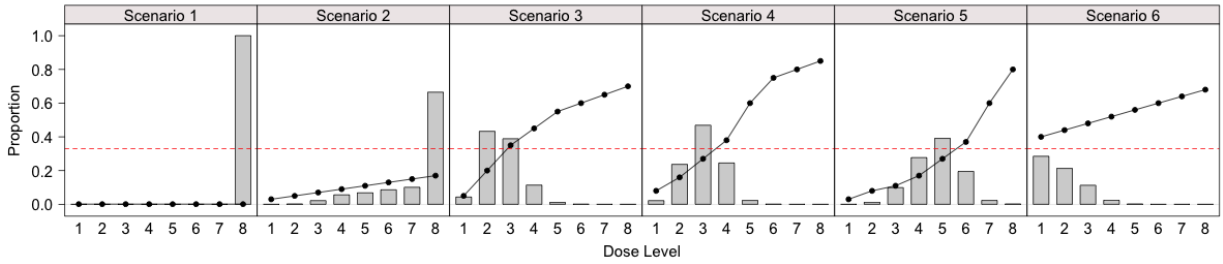
In scenarios 1-5, the dose that is the true MTD has the highest probability of being selected, and also receives a large proportion of patients. Doses below the MTD tend to receive a fair number of patients as well due to the expected rate of enrollment and the size of the allowable queue. In the last scenario, no doses are safe, and the trial stops without identifying an MTD in 36.4% of trials.

Table 5.2 Operating Characteristics

Scenario	Parameter	500	750	1000	1250	1500	1750	2000	2250	None
1	Pr(MTD)	0.000	0.000	0.000	0.000	0.000	0.000	0.000	***1.000***	0.000
	Mean N	0.0	0.0	6.5	6.5	6.5	6.5	6.5	***10.0***	
2	Pr(MTD)	0.000	0.002	0.022	0.056	0.068	0.086	0.101	***0.665***	0.000
	Mean N	0.1	0.2	7.0	6.5	6.3	5.9	5.4	***6.4***	
3	Pr(MTD)	0.043	***0.433***	0.389	0.114	0.011	0.001	0.000	0.000	0.008
	Mean N	1.7	***4.5***	8.3	2.4	0.4	0.0	0.0	0.0	
4	Pr(MTD)	0.022	0.237	***0.469***	0.245	0.023	0.001	0.000	0.000	0.004
	Mean N	1.0	2.9	***8.6***	4.0	0.9	0.1	0.0	0.0	
5	Pr(MTD)	0.000	0.012	0.099	0.277	***0.391***	0.195	0.023	0.002	0.001
	Mean N	0.1	0.5	7.5	6.8	***5.9***	3.3	0.9	0.1	
6	Pr(MTD)	0.285	0.213	0.113	0.024	0.002	0.000	0.000	0.000	0.364
	Mean N	4.9	3.7	6.9	0.9	0.1	0.0	0.0	0.0	

Figure 5.2 shows a graphical representation of the operating characteristics. The height of each bar represents the proportion of simulated trials for which that dose was selected as the MTD. The true underlying dose-toxicity curve is overlaid on the plot, with a dashed red reference line depicting the target DLT rate of 33%.

Figure 5.2 MTD Selection Proportions



Appendix D
Study CO-1686-008 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 8 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.

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.[24] Acetylator status is currently available for 635 patients. Additional testing will be completed as additional samples are received.

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

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

Appendix D, Table 1. Grade 3 or Greater Treatment-emergent Adverse Events by Acetylator Status

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

Abbreviation: CT=combined terms.

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

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

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

	Overall (N = 635)		
	Slow (n = 300)	**Intermediate (n = 259)**	**Rapid (n = 76)**
QTcF Post-baseline ≥ 450 msec	198 (66%)	131 (51%)	34 (45%)
QTcF Post-baseline ≥ 481 msec	92 (31%)	44 (17%)	7 (9%)
QTcF Post-baseline ≥ 501 msec	59 (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. No patient will commence treatment under this amendment until appropriate IEC/IRB approval of the study protocol has been received.

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 21-day cycle. Dosing will be delayed or decreased according to protocol-specified toxicity criteria (Section 7.4.3). 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. 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 7.4.3) 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.

Formal safety data reviews will continue approximately every 6 months once enrollment is completed and as long as patients remain on treatment. The review committee includes external experts and sponsor personnel. The external experts will include, but not be limited to, the coordinating PIs of the study. The sponsor's reviewers will include the Medical Monitor and additional Clovis medical experts, and a biostatistician. The protocol will be amended as appropriate to incorporate additional patient safety monitoring if new safety signals or a change in risk:benefit are noted at any review.

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-1686-008 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:

- Disease progression (PD) based on tumor scans or clinical status assessed by the investigator.
  - 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)
- Unacceptable toxicity.
- Patient withdrawal of consent to further treatment.
- Major noncompliance that may affect patient safety.
- Pregnancy.
- Investigator decision.

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

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

STUDY PROCEDURES

Schedule of Assessments

The procedures and assessments to be performed are outlined in the Schedule of Assessments presented in Appendix D, 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 D, Table 4: Protocol CO-1686-008 Schedule of Assessments – Extension Phase (Phase 1 and Phase 2 Patients)

	Prior to beginning Amendment 8 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
Local fasting Serum Chemistry[d]		X	X
Local Hematology[d]		X	X
Adverse Events (AE) Monitoring[e]		X	X
Patient Diary[f]		X	X
CO-1686 Dispensing / Administration		X	
ECG Assessments using central ECG machine[g]		X	X
Tumor Scans[h]	To be performed per institutional standard of care or every 3 cycles; scans are not required at the End of Treatment Visit		
Blood for CYP Evaluation (Optional Sampling)[i]		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. Samples should be analyzed by local laboratory.

[e] = Patients will be monitored for AEs from the time the first dose of CO-1686 is administered through 28 days after the last dose.

[f]= Patient diaries should be collected and reviewed for compliance at each visit. No diary will be dispensed at end of treatment.

[g]=12-lead ECG (in triplicate, 10-sec tracings > 2 min apart) prior to dosing up to and including Cycle 12, at a minimum. For patients who are ongoing at this time and for whom QT has been < 470 ms throughout the study, ECG monitoring may be subsequently taken every 3rd cycle thereafter. ECGs will be performed and interpreted locally for patient care decisions; however, tracings should be submitted to the central lab for independent evaluation.

[h]=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.

[i]=Only one 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:

The following procedures are conducted before dosing with CO-1686:

- 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 machineprior to dosing up to and including Cycle 12. 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 (includes fasting glucose) HbA1c will be measured every other cycle (Day 1 of Cycle 3, 5, 7 etc).
- Hematology
- Concomitant medications and procedures
- AE monitoring
- Collection and review of patient diary
- Dispense capsules or tablets to 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.
- Dispense patient diary to patient
- (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

The following procedure is conducted irrespective of dosing time:

- Tumor scans per institutional standard of care or every 3 cycles (between Days 14 and 21). 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.

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
- 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