A phase 2, open-label, multicenter, safety and efficacy study of oral lucitanib in patients with FGF aberrant metastatic breast cancer

Protocol Number:	CO-3810-025
Investigational Product:	Lucitanib (S 80881/CO-3810)
IND Number:	[redacted]
Development Phase:	Phase 2
Indication Studied:	Fibroblast growth factor receptor 1 (*FGFR1*)- or 11q (FGF3, FGF4, Cyclin D1, or FGF19)-amplified metastatic breast cancer
Sponsor Name and Address:	Clovis Oncology, Inc. 5500 Flatiron Parkway Boulder, CO 80301 USA [redacted]
Responsible Medical Officer:	[redacted]
Compliance Statement:	This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, clinical research guidelines established by the Code of Federal Regulations (Title 21, CFR Parts 50, 56, and 312), and ICH GCP Guidelines. Essential study documents will be archived in accordance with applicable regulations.

[redacted]

[redacted]

CONFIDENTIALITY STATEMENT

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Protocol Approval Signature Page

Protocol:	CO-3810-025
Title:	A phase 2, open-label, multicenter, safety and efficacy study of oral lucitanib in patients with FGF aberrant metastatic breast cancer
Date:	27 January 2016
Version:	[redacted]

Reviewed and Approved by:

[redacted]

Protocol Acceptance Form

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Title: A phase 2, open-label, multicenter, safety and efficacy study of oral lucitanib in patients with FGF aberrant metastatic breast cancer

Date: 27 January 2016

Version: [redacted]

Reviewed and Approved by:

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

Investigator's Signature | Date

Name (printed)

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1 SYNOPSIS

Protocol Number	CO-3810-025
Title	A phase 2, open-label, multicenter, safety and efficacy study of oral lucitanib in patients with FGF aberrant metastatic breast cancer
Phase	Phase 2
Introduction	Lucitanib is a potent, orally available selective inhibitor of the tyrosine kinase activity of fibroblast growth factor receptors (FGFR1–3), vascular endothelial growth factor receptors (VEGFR1–3), and platelet-derived growth factor receptors alpha and beta (PDGFRα/β) with activity in relevant cell lines and animal models. A phase 1/2 clinical trial demonstrated multiple objective responses in women with *FGFR1*- or 11q (FGF3, FGF4, Cyclin D1, or FGF19)-amplified breast cancer (Response Evaluation Criteria in Solid Tumors [RECIST] objective response rate [ORR] 50%). The 11q amplicon contains genes for FGF3, FGF4, and FGF19 proteins that are ligands of *FGFR1*. These responses are notable in breast cancer where FGF-aberrancy is recognized as an early, common, and stable event in breast carcinogenesis. Further, preclinical evidence supports up-regulation of FGF-related activity as a mechanism of resistance to endocrine therapy in estrogen receptor positive (ER+) breast cancer. Toxicities are those typically seen with potent VEGFR inhibitors, such as hypertension, hypothyroidism, and proteinuria. Other common adverse events (AEs) include asthenia, thrombotic microangiopathy (TMA), thrombocytopenia, abdominal pain, anorexia, nausea, vomiting, and diarrhea. Based on the phase 1/2 study results, 15 mg daily was previously advanced as the recommended phase 2 dose of lucitanib. However, interim data from ongoing lucitanib studies has shown that the daily dose of 15 mg is difficult for many patients to sustain and dose reductions have been frequently required. Further, clinical responses have been observed at both 10 mg and 15 mg daily dosing schedules. Therefore, beginning in mid-2015, the decision was made to implement lucitanib at 10 mg daily across the clinical development program. Under prior versions of this protocol, patients with *FGFR1* or 11q amplification were randomized to receive either 10 (Cohort A) or 15 mg (Cohort B) of lucitanib daily. With this version of the protocol (amendment #4), randomization has been removed. Instead, enrollment to the 15 mg cohort (Cohort B) will stop and enrollment to the 10 mg cohort (Cohort A) will continue. Likewise, Patients without *FGFR1* or 11q amplification (Cohort C) were previously enrolled to receive 15 mg of lucitanib daily. With this version of the protocol (amendment #4) Cohort C patients will receive 10 mg daily.
Planned Number of Patients	*FGFR1*-amplified and 11q-amplified patients will be enrolled* as follows: • Cohort A (10 mg): approximately 80 patients (no more than forty 11q-amplified patients) • Cohort C (10 mg): up to 40 patients *1:1 randomization to Cohorts A and B was removed with amendment #4. Up to 80 patients were enrolled into Cohort B under prior versions of this

	protocol.	
Planned Number of Sites	Approximately 30–40 investigative sites in the United States. Accrual to Cohort C will be limited to 10–15 sites participating in the pharmacokinetics (PK) sub study, until enrollment in the sub study has been filled.	
Study Objectives and Endpoints	**Primary Objective**	**Primary Endpoint**
	To estimate the anti-tumor efficacy of oral single-agent lucitanib as measured by investigator assessed PFS, when administered to patients with *FGFR1*- or 11q-amplified breast cancer after failure of currently available standard therapies	PFS per RECIST Version 1.1 as determined by the investigator
	Secondary Objectives	**Secondary Endpoints**
	To estimate anti-tumor efficacy of oral single-agent lucitanib as measured by ORR, duration of response (DR), disease control rate (DCR), and overall survival (OS)	• ORR according to RECIST Version 1.1 • DR and DCR according to RECIST Version 1.1 • OS
	To estimate patient-reported outcomes (PRO) following treatment with lucitanib	Change from baseline in PRO using the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire
	To evaluate safety and tolerability of lucitanib	Treatment emergent AEs, laboratory abnormalities, physical examinations including vital signs and electrocardiogram (ECG) abnormalities
	To assess the comparative pharmacokinetics (PK) of the lucitanib tablet formulation with the lucitanib capsule formulation	PK parameters including area under the concentration curve from time zero to time t (AUC_{0-t}), maximum concentration (C_{max}), time to maximum concentration (t_{max}), elimination half-life ($t_{1/2}$), volume of distribution at steady state (V_{SS}/F), and total plasma clearance (Cl/F) for lucitanib, if data allow
	Exploratory Objectives	**Exploratory Endpoints**
	To explore tumor tissue and blood-based biomarkers that may be predictive of response or primary resistance to treatment with lucitanib	• Concordance of tumor tissue *FGFR1* and 11q amplification assessed across different technical platforms (fluorescence in-situ hybridization [FISH], Next Generation Sequencing [NGS], comparative genomic hybridization [CGH],

Study Objectives and Endpoints (continued)		chromogenic in-situ hybridization [CISH], quantitative polymerase chain reaction [qPCR], or circulating tumor cells [CTCs/ctDNA]) • Exploration of different cut-off values for determining *FGFR1* and 11q amplification in tumor tissue by FISH and correlation with clinical efficacy • Ribonucleic acid (RNA) expression of *FGFR1*, FGF3/4/19, and additional FGF family members; correlation with *FGFR1* and 11q amplification status and clinical efficacy • Protein expression of *FGFR1* as determined by immunohistochemistry (IHC) in tumor tissue; correlation with *FGFR1* amplification status • Genomic analysis of circulating tumor DNA (ctDNA)
	To explore blood-based pharmacodynamic (PD) biomarkers of lucitanib activity	• PD biomarker analysis measurement of circulating plasma biomarker levels including but not limited to FGF-2, FGF-23, sVEGFR1, VEGF-A, sCSF-1R, and CSF-1 • Pharmacogenomic analysis of variations in genes encoding proteins involved in absorption/distribution/ metabolism/excretion (ADME)
	To determine pharmacokinetics (PK) of lucitanib in this patient population using population pharmacokinetic (POPPK) methods and explore correlations between exposure, response, and/or safety findings	Plasma PK parameters for lucitanib based on sparse sampling for POPPK analysis

Study Design	This is a Phase 2, open-label, multicenter study evaluating the efficacy and safety of lucitanib administered orally to patients with metastatic breast cancer. Patients with metastatic breast cancer will be enrolled into one of two different cohorts (Cohort A: FGF-amplified or Cohort C: FGF non-amplified) both receiving 10 mg daily. For patients with local *FGFR1* or 11q test results, a central laboratory will confirm the presence or absence of the *FGFR1* or 11q amplification. Central testing prior to enrollment for these patients is not required for study enrollment. Patients with local *FGFR1* and 11q results for whom central reading does not confirm amplification status can continue the study at the discretion of the investigator if clinical benefit is observed. If there are a significant number of patients with discordant local and central testing results, additional patients may be enrolled. For patients without a local *FGFR1* or 11q test result, tissue must be submitted for central testing under a prescreening process. Under the prescreening process, a confirmed central laboratory test result is required for screening and enrollment into Cohort A (*FGFR1*- or 11q-amplified) or enrollment into Cohort C (FGF non-amplified). Up to 20 enrolled patients will participate in a PK sub-study to assess the comparative PK of the lucitanib tablet formulation with the lucitanib capsule formulation. Cycles are defined as 28 days in duration. Protocol-specified treatment will continue until there is clinical tumor progression or unacceptable toxicity. Patients will undergo serial assessments for anti-tumor efficacy, drug safety, and PROs. Sparse blood sampling for POPPK analyses will be conducted in all patients treated with lucitanib. Tumor scans will be acquired by the investigative site and evaluated locally for patient treatment decisions. Patients who provide additional consent will undergo an optional post-treatment biopsy for PD analyses. AEs will be assessed from the time of first dose of lucitanib through 28 days after the last protocol-specified treatment administration. For the first 6 cycles, patients will undergo tumor scans within 28 days prior to the first drug administration, 4 weeks after first drug administration, and every 8 weeks thereafter. Patients with stable disease or better after their Cycle 6 scan will continue to have tumor scans every 12 ± 1 weeks until tumor progression. All patients will be followed at approximately two monthly intervals to determine survival status, until death or sponsor decision to end the trial, whichever comes first. After discontinuation of protocol-specified treatment, subsequent anticancer therapy use will be recorded.
Study Population	<u>Inclusion Criteria</u> 1. Histologically or cytologically confirmed metastatic breast cancer relapsed or refractory to approved standard available treatment ° Specifically, patients with human epidermal growth factor receptor 2 (HER2)-positive disease, as defined by the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines, must have exhausted approved HER2-directed therapies prior to enrollment 2. Prior treatment with standard first line therapy in the metastatic setting

Study Population (continued)	3. *FGFR1* amplification or 11q amplification status determined on the most recent tumor tissue available, or detected in blood using validated methods for detecting circulating tumor cells (CTCs) or ctDNA: a) Patients in Cohorts A and B: *FGFR1*- or 11q-amplified b) Patients in Cohort C: neither *FGFR1*- nor 11q-amplified Patient amplification status will be based on: ° local assessment by FISH, NGS, CGH, CISH, or qPCR; or ° local assessment in blood using validated methods for detecting circulating tumor cells (CTCs) or ctDNA; or ° central assessment by FISH, as confirmed by a prescreening process 4. Availability of formalin-fixed paraffin-embedded (FFPE) tumor tissue sufficient for the central confirmation by FISH of *FGFR1* amplification or 11q amplification status. Detailed sample handling instructions are provided in the Laboratory Manual 5. Demonstrated progression of disease by radiological or clinical assessment ° Measurable disease according to RECIST Version 1.1 is NOT required for enrollment 6. Patient aged ≥18 years old 7. Eastern Cooperative Oncology group (ECOG) Performance status 0 or 1 8. Estimated life expectancy >6 months 9. Normal left ventricular function defined as a left ventricular ejection fraction (LVEF) ≥50% by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan 10. Screening for laboratory values within the following parameters: ° Hematology: absolute neutrophil count (ANC) ≥1000/mm^3; platelet count ≥100,000/mm^3; hemoglobin ≥9 g/dL ° Renal function: – Serum creatinine <1.5 mg/dL or creatinine clearance >45 mL/min (Modification of Diet in Renal Disease formula [MDRD]) – Dipstick protein measurement <2+. If dipstick ≥2+ then perform 24-hour urine protein measurements and if proteinuria <300 mg patient is eligible for inclusion ° Liver function tests: total bilirubin ≤1.5 upper limit of normal (ULN; unless evidence of Gilbert's disease confirmed by uridine diphosphate-glucuronyltransferase [UGT] polymorphism); aspartate transaminase (AST) and alanine transaminase (ALT) ≤3 ULN; AST and ALT ≤5 ULN in case of liver metastases 11. For women of childbearing potential, a negative pregnancy test within 7 days prior to initiation of the study drug 12. Willingness to use an effective contraceptive method during the study and up to six months after the last dose is administered. Effective methods include the following: non-hormonal intrauterine device, barrier method (condoms, diaphragm) also in conjugation with spermicidal jelly, or total abstinence. Oral, injectable, or implant hormonal contraceptives are discouraged

Study Population (continued)	13. Written consent on an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved Informed Consent Form (ICF) prior to any protocol-specific evaluation Exclusion Criteria Any of the following criteria will exclude patients from study participation: 1. Current or recent treatment with biologic anticancer therapies. Required washout for prior biologic anticancer therapies: ° 3 months for bevacizumab ° 28 days or five half-lives, whichever is shorter, for all other biologic therapies 2. Ongoing AEs from prior anticancer therapies, including radiation, targeted or cytotoxic therapies without resolution of any Grade 2 or greater side effects to Grade ≤1 3. Current treatment with any prohibited medications associated with prolongation of QT interval and known risk of Torsades de Pointes (see Appendix C) 4. Active central nervous system (CNS) metastases, as indicated by clinical symptoms, cerebral edema, and/or progressive growth (patients with history of CNS metastases or cord compression are eligible if they are clinically stable for at least 4 weeks before first dose of lucitanib and do not require high-dose steroid treatment) 5. History of clinically significant or uncontrolled cardiac disease, including congestive heart failure (HF; New York Heart Association functional classification ≥3), angina, myocardial infarction within 6 months, or ventricular arrhythmia 6. QT_C prolongation (defined as a QT_C interval >470 msec according to Fridericia's correction) 7. Uncontrolled hypertension (defined as systolic blood pressure [SBP] ≥140 mmHg and/or diastolic blood pressure [DBP] ≥90 mmHg with optimized anti-hypertensive therapy) ° The requirement for >2 anti-hypertensives to control hypertension at time of enrollment is exclusionary 8. Active second malignancy, i.e., patient known to have potentially fatal cancer present for which he/she may be (but is 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 (BMT) >2 years prior 9. Uncontrolled hypothyroidism defined as serum thyroid stimulating hormone (TSH) higher than 5 mIU/mL while receiving optimized thyroid hormone replacement therapy 10. Patient with history of thrombotic disorders: ° Any history of venous thrombotic events, deep vein thrombosis (with the exception of catheter related deep vein thrombosis), or pulmonary embolism within 6 months prior to the first dose of lucitanib ° Any history of arterial thrombotic events, cerebrovascular

	accident, or transient ischemic accident within 6 months prior to the first dose of lucitanib ° Any peripheral vascular disease or vasculitis which required treatment within 6 months prior to the first dose of lucitanib ° Patient with hereditary risk factors of thromboembolic events (e.g., mutation of the Factor V of Leiden) 11. Received administration of strong inhibitors of CYP2C8 or CYP3A4 or strong inducers of CYP3A4 ≤7 days prior to first dose of lucitanib or have on-going requirements for these medications (Appendix E) 12. Received investigational treatment within 28 days prior to enrollment in this study 13. Non-study related minor surgical procedures ≤14 days prior to administration of lucitanib. In all cases, the patient must be sufficiently recovered and stable before treatment administration 14. History of major surgical procedure or significant trauma within 28 days prior to lucitanib. In all cases, the patient must be sufficiently recovered and stable before treatment administration 15. Females who are pregnant or breastfeeding 16. Presence of any serious or unstable concomitant systemic disorder incompatible with the clinical study (e.g., substance abuse, uncontrolled psychiatric condition, uncontrolled intercurrent illness including active infection, arterial thrombosis, and symptomatic pulmonary embolism) 17. Foreseeable poor compliance to the study procedures 18. Any other reason the investigator considers the patient should not participate in the study
Study Treatment	Lucitanib (capsule or tablet formulation) will be administered at a dose of 10 mg once daily and swallowed with water (240 mL or 8 ounces). Patients should take lucitanib at approximately the same time each day, on an empty stomach, at least 2 hours before and 2 hours after a meal (fasting window is a total of 4 hours). Patients enrolled in the PK sub study will receive a single dose of lucitanib in a tablet formulation on Day –7 followed by a single dose of lucitanib in a capsule formulation on Day 1. From Cycle 1 Day 2 onward, lucitanib may be given as capsules or tablets, as per sponsor guidance.
Dose-Modification Criteria and Toxicity Management	Patients are allowed dose reductions by 2.5 mg increments after Cycle 1, Day 1 (C1D1). Dose re-escalation in 2.5 mg increments is permitted at the start of a cycle as long as the cause of the dose reduction has resolved to Grade 1 or better (see Section 7.4.8). Dose escalations above the starting dose are not permitted. <u>Management of hypertension</u> Hypertension should be closely monitored and treated if required. Abnormal blood pressure (BP) measurements in clinic should be repeated within an hour to confirm findings. Additionally, patients should be instructed to self-measure their BP at home at least two times per week while receiving lucitanib treatment. Patient-monitored BP should be followed by the investigator at all clinic

<table>
<tr><td rowspan="6">Dose-Modification Criteria and Toxicity Management (continued)</td><td colspan="2">visits to evaluate the effectiveness of anti-hypertensive treatment.

The early detection and effective management of hypertension are important to minimize risk for the patient and the need for lucitanib dose interruptions and reductions.

The following treatment and lucitanib dose adjustments algorithm should be followed in case hypertension is encountered:</td></tr>
<tr><td>Observation</td><td>Action</td></tr>
<tr><td rowspan="2">Patient experiences hypertension for the first time or patient with previously controlled hypertension experiences worsening in BP values with SBP from 140 to 159 mmHg and/or DBP from 90 to 99 mmHg.</td><td>Patients without pre-existing hypertension</td></tr>
<tr><td>Initiate anti-hypertensive therapy immediately.

Immediate use of two anti-hypertensive agents can be considered in case of rapid elevation of BP. The anti-hypertensive therapy can be adjusted over a period of 14 days. The patient should be followed by the investigator at least once a week to evaluate the response to the anti-hypertensive treatment. During this period, interruption of lucitanib or dose modification is not necessary.

If BP decreases to < 140/90 mmHg in 14 days, continue lucitanib at the same dose.</td></tr>
<tr><td rowspan="2"></td><td>Patients with pre-existing hypertension</td></tr>
<tr><td>Intensify/adapt current any current anti-hypertensive treatment. Immediate dose and therapeutic class optimization should be performed. Up to three anti-hypertensive agents should be considered.

The anti-hypertensive agent can be adjusted over a period of 14 days. The patient should be followed by the investigator at least once a week to evaluate the response to anti-hypertensive treatment. During this period, interruption of lucitanib or dose modification is not necessary.

If BP decreases to < 140/90 mmHg within 14 days, continue lucitanib at the same dose.</td></tr>
<tr><td>Dose-Modification Criteria and Toxicity Management</td><td>In case of persisting hypertension with SBP from 140 to 159 mmHg and/or DBP from 90 to 99 mmHg despite optimized anti-hypertensive treatment after 14 days.</td><td>Reduce lucitanib dose by 2.5 mg.

Ensure adequate control of BP below 140/90 mmHg including increasing the dose of the current anti-hypertensive agent(s) (if appropriate) and/or initiation of additional anti-hypertensive agents, if</td></tr>
</table>

(continued)		required. Allow up to 14 days for BP to be controlled. If BP does not reduce to < 140/90 mmHg after 14 days, lucitanib should be reduced again by 2.5 mg (to the next dose level). Allow an additional 14 days for BP to be controlled. If BP does not reduce to < 140/90 mmHg within the additional 14 days, lucitanib should be interrupted for up to 14 days. If BP decreases to < 140/90 mmHg in 14 days, restart lucitanib at the last dose. If BP remains at ≥ 140/90 mmHg after 14 days, sponsor approval is required prior to re-initiating lucitanib treatment.
	In case of confirmed hypertension with SBP equal or above 160 mmHg, and/or DBP equal or above 100 mmHg.	**Patients presenting with no hypertension-related symptoms & no more than one risk factor[1]**
		Continue lucitanib therapy. Immediately start anti-hypertensive treatment or optimize current anti-hypertensive treatment. Allow up to 4 days for BP to be controlled (BP < 140/90 mmHg), with close follow-up by the treating physician. If BP does not reduce to ≤ 160/100 mmHg within 4 days, lucitanib should be reduced by 2.5 mg. If BP does not reduce to ≤ 160/100 mmHg within 4 additional days despite lucitanib dose reduction and optimal anti-hypertensive therapy, lucitanib should be interrupted. If BP decreases to < 140/90 mmHg within 14 days, resume lucitanib at next lower dose. If BP is not controlled (< 140/90 mmHg) within 14 days after interruption of lucitanib and despite optimal anti-hypertensive treatment, lucitanib should be permanently discontinued.
Dose-Modification Criteria and Toxicity Management		

(continued)

	Patients with mildly symptomatic hypertension[2] (outside of cardiovascular, cerebral, or major renal complications) **or several risk factors[1] or already receiving two anti-hypertensive agents**
	Temporarily interrupt lucitanib therapy. Immediate use of two anti-hypertensive agents may be considered in patients with no history of hypertension. For patients already on two anti-hypertensive agents, modification of the current anti-hypertensive therapy and/or adding a third agent should be considered. The patient should be followed by the investigator closely to evaluate the response to anti-hypertensive treatment. Allow up to 14 days for BP to be controlled (BP < 140/90 mmHg). If BP decreases to < 140/90 mmHg within 14 days, resume lucitanib at next lower dose. If BP does not reduce to < 140/90 mmHg within 14 days, lucitanib should be permanently discontinued.
In case of confirmed hypertensive crisis with life-threatening consequences. Hypertensive crisis is defined as an increase in BP (≥ 180 mmHg SBP and/or ≥ 120 mmHg DBP) that can lead to life-threating consequences (e.g., cerebral stroke).	Lucitanib must be permanently discontinued.

[1]Risk factors include those comorbidities that in the opinion of the investigator would increase the patient's risk of hypertension-related complications, e.g., diabetes, coronary artery disease
[2] Mildly symptomatic hypertension defined as symptoms of headache, facial flushing, etc in the absence of additional cardiac or neurological findings

Pharmacological management should be based on the investigator's judgment and no definite recommendations for an anti-hypertensive agent can be made. However, calcium channel blockers may be preferred as initial treatment based on their rapidity of action and safety profile. Angiotensin Converting Enzyme (ACE) inhibitors can be considered in case of concomitant proteinuria. In case of rapid elevation of BP, two anti-hypertensive agents should be considered. The use of three anti-hypertensive agents such as concomitant use of a renin-angiotensin system inhibitor, calcium channel blocker, and diuretic drug may be considered based on the investigator's decision. In that case, close surveillance of kidney function and electrolytes is strongly recommended.

Dose-Modification Criteria and Toxicity Management (continued)

Management of proteinuria

Patients will be monitored for proteinuria by dipstick every two weeks during Cycle 1 and Cycle 2 and every 28 days thereafter. Patients with early signs of proteinuria by dipstick (2+) should be closely monitored and proteinuria evaluated quantitatively (24 hours protein excretion or protein-to-creatinine ratio). Additional safety monitoring should be performed as clinically indicated including tests for the assessment of free/conjugated bilirubin, haptoglobin N, schizocytes, or renal biopsy.

The following treatment and lucitanib dose adjustments algorithm should be followed in case proteinuria is encountered:

In case of first onset of proteinuria ≥Grade 2 (i.e., ≥1 g in 24 hours by quantitative assessments)	Lucitanib treatment should be withheld and proteinuria monitored by dipstick twice weekly. Upon recovery of proteinuria to Grade ≤1 (1+ by dipstick or urinary protein <1.0 g/24 hours), lucitanib treatment should be resumed at the same dose and dipstick monitoring should continue.
In case of second onset of proteinuria ≥Grade 2	Withhold the drug and perform a quantitative assessment of 24-hour urinary protein. Upon recovery, the lucitanib treatment should be resumed with a 2.5 mg dose reduction (e.g., 10 mg to 7.5 mg)
In case of third onset of proteinuria ≥Grade 2	Repeat assessments and dose modifications as outlined above (e.g., 7.5 mg to 5 mg)
In case of fourth onset of proteinuria ≥Grade 2	If proteinuria ≥ Grade 2 recurs following dose reductions to 5 mg, or if there is no recovery within 30 days, discontinue treatment permanently

Management of sub-clinical hypothyroidism

Plasma TSH and thyroid hormones levels should be measured, per protocol. Treatment with levothyroxine 50 µg/day is recommended for patients with TSH values above 5 mIU/L, even if triiodothyronine (T3) and thyroxine (T4) are normal. The treatment with lucitanib can continue at the same dose.

Management of LVEF

LVEF will be assessed by ECHO or MUGA. It is recommended to use the same technique for a given patient throughout the whole study duration. In case of HF symptoms or modification on imaging from baseline the following rules must be applied:

- No signs of HF and LVEF ≥45% OR absolute drop from baseline ≤15 EF % points. Continue lucitanib at the same dose level and repeat LVEF assessment per protocol
- Patient is symptomatic OR LVEF <45% OR absolute drop from baseline >15 EF % points. Hold lucitanib until resolution (LVEF ≥50% **and**

Dose-Modification Criteria and Toxicity Management (continued)	asymptomatic). If resolution occurs within 3 weeks, lucitanib can be resumed at a reduced dose by 2.5 mg increments, as described above, otherwise withdraw lucitanib permanently • No recovery OR LVEF <20%. Discontinue lucitanib permanently and follow-up the patient Management of QT_C prolongation In case Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 prolongation of the QT_CF (Fridericia correction) interval >500 msec, lucitanib treatment must be withheld. Serum calcium, phosphorus, potassium, and magnesium levels should be analyzed, and levels should be corrected to within normal limits if needed. In all cases a second ECG must be carried out to confirm the QT_CF prolongation >500 msec within 1 hour of the initial ECG. Concomitant medication list should be reviewed. Once QT_CF prolongation has resolved, lucitanib may be restarted at a 2.5 mg lower dose. Further dose reductions are permitted, as described above. Grade 4 QT_C prolongation (QT_C >501 msec or >60 msec change from baseline and Torsades de Pointes or polymorphic ventricular tachycardia or symptoms of serious arrhythmia) should result in permanent discontinuation of lucitanib. Management of liver toxicities In case of Grade 3 increases in ALT and AST, the dose will be withheld until recovery to Grade 2. If recovery occurs within 14 days, treatment will be resumed at the same dose level. If no recovery occurs within 14 days, the treatment will be resumed at a 2.5 mg lower dose upon recovery. Further dose reductions are permitted, as described above. In case of repeated events at 5 mg or absence of recovery to Grade 2 within 7 days, lucitanib will be stopped permanently. Management of Posterior Reversible Encephalopathy Syndrome (PRES) If a patient presents with symptoms suggestive of posterior reversible encephalopathy syndrome (PRES) (e.g., persisting headache not responsive to usual analgesics, confusion, visual symptoms, seizures and coma), immediately interrupt lucitanib treatment and consider performing all relevant clinical and radiological examinations (e.g., neurological consultation, MRI) in order to ensure early diagnosis and treatment of this syndrome. A follow-up MRI should be performed in order to confirm the diagnosis of PRES, and if confirmed, lucitanib treatment must be permanently discontinued. Management of other toxicities For other Grade 3 or 4 hematologic and non-hematologic toxicities (except for alopecia), lucitanib treatment should be withheld until recovery to Grade 2 for hematological or Grade 1 for non-hematological toxicity. Upon recovery, the drug may be resumed at a 2.5 mg lower dose. Once the dose has been reduced within a treatment cycle, treatment continues at that dose level; no dose escalation is possible within a cycle. If a patient continues to experience toxicity after all allowed dose reduction steps as described above (i.e., after a patient has been dose-reduced from starting dose to 5 mg/day), or if dosing with lucitanib is interrupted for >14 consecutive days due to toxicity, treatment should be permanently discontinued, unless otherwise

Dose-Modification Criteria and Toxicity Management (continued)	agreed between the investigator and the sponsor. In the event of Grade 3 or 4 nausea and vomiting, antiemetics should be used. If, despite maximal antiemetic use, Grade 3 or 4 nausea or vomiting persists, lucitanib treatment should be withheld until recovery and dose reduction and discontinuation should follow the same paradigm as recommended for other Grade 3 and 4 non-hematologic toxicities.
Concomitant Medications	**Permitted concomitant medication and medication that should be used with caution:** • Lucitanib is highly bound to plasma proteins; therefore, use caution with warfarin which is also highly bound to plasma protein and with a narrow therapeutic window • Supportive care (e.g., antiemetics, analgesics for pain control) may be used at the investigator's discretion and in accordance with institutional procedures • Drugs with potential to cause prolonged QT interval and/or possible risk or conditional risk to cause Torsades de Pointes must be used with caution (see Appendix C) • Considering the risk of drug-drug interactions, concomitant use of moderate inhibitors of CYP2C8 or CYP3A4 are not recommended during the study (see Appendix E) **Prohibited concomitant medications:** • Systemic anticancer therapy (e.g., hormonal therapy, immune therapy, targeted therapy), except for bisphosphonates and denosumab in patients with bone metastases • Prior treatment with bevacizumab within 3 months prior to the first dose of lucitanib • Radiotherapy during the treatment period is prohibited. Palliative bone radiotherapy at focal sites can be allowed during the screening period, before lucitanib intake and providing recovery is achieved before study drug initiation • Drugs known to cause prolonged QT interval and/or known risk of causing Torsades de Pointes (see Appendix C) • Strong inhibitors of CYP2C8 or CYP3A4 are contraindicated during the study. Should acute treatment with a strong inhibitor be deemed necessary, lucitanib must be temporarily withheld. Lucitanib may be resumed after a minimum of seven days of ending acute treatment with a strong inhibitor of CYP2C8 or CYP3A4. • Co-administration of strong inducers of CYP3A4 (Appendix E) are not permitted at any time during treatment with lucitanib

Withdrawal Criteria	A patient must be discontinued from protocol-prescribed therapy if <u>any</u> 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, unless in the opinion of the investigator, the patient has indolent progression with evidence of continued clinical benefit from treatment. This must be approved by the sponsor and reviewed on a case by case basis • Any event, adverse or otherwise, that, in the opinion of the investigator, would pose an unacceptable safety risk to the patient • An intercurrent illness that, in the opinion of the investigator, would affect assessments of the clinical status to a significant degree and requires discontinuation of therapy • A positive pregnancy test at any time during the study • Major non-compliance that may affect patient safety • Investigator decision After stopping protocol-specified treatment, all patients will remain in the study and will be followed for safety (through 28 days after last dose), and for survival status by telephone (at approximately two monthly intervals, until death).
Efficacy Assessments	Efficacy measures will include tumor assessments, consisting of clinical examination and computed tomography (CT) scans of the chest, abdomen, and pelvis with intravenous contrast and appropriate slice thickness per RECIST Version 1.1; other alternative studies (magnetic resonance imaging [MRI] and X-ray) may be performed if clinically indicated. Brain imaging is required at baseline. Patients with brain lesions detected at baseline will require repeat brain imaging as part of the follow-up tumor assessments. The first on-treatment scan should be completed on Cycle 2, Day 1, and every 8 ± 1 weeks through Cycle 6 (i.e., C4D1, C6D1). Thereafter, scans should be completed every 12 ± 1 weeks (i.e., C9D1, C12D1, C15D1, etc.) until disease progression. All patients must have scans to confirm radiographic progression. Patients that permanently discontinue lucitanib should continue scans until radiographic disease progression. Copies of tumor scans will be collected centrally to facilitate independent evaluation if subsequently required.
Safety Assessments	Safety measures will include: • AEs • Hematology, including reticulocyte count, prothrombin time (PT)/partial thromboplastin time (PTT); clinical chemistry including TSH, T3, and T4; and urinalysis • 12-lead ECGs • ECHOs • Vital signs and body weight • Concomitant medications/procedures • ECOG performance status • Lucitanib dose modifications (reductions)

Biomarker Assessments	• *FGFR1* and 11q amplification status in tumor tissue assessed by FISH, CISH, and NGS • RNA expression of various lucitanib-related genes including, but not limited to *FGFR1,* FGF3/4/19, and additional FGF family members • Protein expression of FGFR1 as determined by IHC • Genomic analysis of ctDNA
Pharmacogenomic Assessments	Analysis of inter-patient variation in genes encoding proteins involved in drug ADME.
Sparse PK Assessments (All Cohorts)	Plasma levels of lucitanib will be measured on pre-dose samples collected on Day 15 of Cycle 1 and Day 1 of Cycles 2, 3, and 5. An additional sample will be collected on Cycle 2, Day 1, 1–3 hours post-dose. Sparse blood sampling for POPPK analyses will be conducted in all patients treated with lucitanib.
PK Sub Study	Patients in Cohorts A or C may be enrolled in the PK sub study, at participating sites, as follows: • Participation in the PK sub study will be optional for patients enrolled into Cohort A • Participation in the PK sub study will be mandatory for patients enrolled into Cohort C until enrollment of the PK sub study is complete PK sampling will be performed at the specified time points on each on the following two days: • Day –7: lucitanib in tablet formulation* • Day 1: lucitanib in capsule formulation* On Day –7 and Day 1, PK specimens will be collected 5–10 min pre-dose and post-dose at 15 min (±2 min), 30 min (±3 min), 1 hr (±5 min), 1.5 hr (±5 min), 2.5 hr (±10 min), 4 hr (±15 min), 6 hr (±15 min), 8 hr (±15 min), 10 hr (±30 min) (optional), and 24 hr (±30 min). PK evaluations will be based on determination of the following parameters for lucitanib including (but not limited to): AUC_{0-t}, C_{max}, t_{max}, $t_{1/2}$, V_{SS}/F, and Cl/F, if data allow. The PK parameters between the tablet and the capsule formulations will be compared. A central laboratory will be used for the bioanalysis of lucitanib. *The dose assigned for patients participating in the PK sub study will be the same for Days –7 and 1 and depends on the version of the amendment approved at the time of patient enrollment (Amendment #3: 15 mg; Amendment #4: 10 mg).
Pharmacodynamic Assessments	Measurement of circulating plasma levels of FGF-2, FGF-23, sVEGFR1, VEGF-A, sCSF-1R, and CSF-1.
Patient-Reported Outcome Assessments	PROs will be measured using the FACT-B questionnaire.

Statistical Procedures	Analysis Populations • Efficacy population: all treated patients who received at least one dose of lucitanib and are confirmed as *FGFR1*- or 11q-amplified per the central laboratory • Safety population: all patients who have received at least one dose of lucitanib Sample Size Justification Approximately 200 patients will be enrolled to the 10 mg and 15 mg daily dosing groups. A total of at least 80 patients in the 10 mg arm is sufficient to reliably estimate the median PFS and 6 month PFS rate in these heavily pre-treated patients. An observed median PFS greater than 4 months or similarly a 6-month PFS rate of at least 40% will be sufficient to consider the 10 mg dose group worthy of further study. Therefore, with at least 80 patients treated at 10 mg, the width of the 90% confidence interval for the 6 month PFS rate will be less than ±10% so that if the observed 6 month rate is 50% then the lower limit on the confidence interval will be greater than 40%. Cohort C will enroll up to 40 patients to evaluate whether the PFS of a FGF non-amplified population is comparable to patients who are *FGFR1*- or 11q-amplified (Cohorts A and B). The same target response of 40% will be used to evaluate Cohort C. With 40 patients, the width of the 90% confidence interval for the 6 month PFS rate will be less than ±15%, so that if the observed 6 month rate is less than 25% then the upper limit on the confidence interval will be less than 40%, which is evidence that subsequent studies of 10 mg should exclude FGF non-amplified patients. Statistical Methods The Kaplan-Meier methodology will be used to summarize the primary endpoint of PFS. The 25th, 50th (median), and 75th percentiles will be presented along with the Kaplan-Meier estimates of the 6 and 12 month PFS rates. The ORR and DCR will be summarized with frequencies and percentages. The DR and OS will be summarized utilizing Kaplan-Meier methodology.
Data Monitoring Committee	A data monitoring committee (DMC) consisting of two external investigator advisors and specified Clovis personnel will meet approximately quarterly after the first patient is enrolled to review the efficacy and safety data. A detailed description of the composition, roles and responsibilities, and functioning of the DMC is provided in the DMC Charter.

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACE	angiotensin converting enzyme
ADME	absorption/distribution/metabolism/excretion
AE	adverse event
ALT	alanine transaminase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate transaminase
AUC	area under the curve
AUC_{0-24}	area under the curve from time zero to 24 hours
AUC_{0-t}	area under the curve from time zero to time t
BMT	bone marrow transplant
BP	blood pressure
BUN	blood urea nitrogen
C1D1	Cycle 1, Day 1
CAP	College of American Pathologists
CBR	clinical benefit rate
CFR	Code of Federal Regulations
CGH	comparative genomic hybridization
CISH	chromogenic in-situ hybridization
Cl/F	total plasma clearance
C_{max}	maximum concentration
CNS	central nervous system
CR	complete response
CRO	contract research organization
CT	computed tomography
CTC	circulating tumor cell
CTCAE	Common Terminology Criteria for Adverse Events (Version 4.03)
ctDNA	circulating tumor DNA
CYP	cytochrome P450
DBP	diastolic blood pressure
DCR	disease control rate
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form

EDC	electronic data capture
ER+	estrogen receptor positive
FACT-B	Functional Assessment of Cancer Therapy-Breast
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptors
FISH	fluorescence in-situ hybridization
GCP	Good Clinical Practice
GI	gastrointestinal
HDPE	high-density polyethylene
HER2	human epidermal growth factor receptor 2
hERG	human ether-a-go-go-related gene
HF	heart failure
HIPAA	Health Information Portability and Accountability Act
HLP	hemolymphopoietic
IB	investigator's brochure
IC_{50}	Concentration of inhibitor required for 50% inhibition
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDMC	Independent Data and Monitoring Committee
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IRB	Institutional Review Board
ITT	Intent to treat
IWRS	Interactive Web Response System
LFT	liver function test
LVEF	left ventricular ejection fraction
MDRD	Modification of Diet in Renal Disease
MRI	magnetic resonance imaging
msec	millisecond
MTD	maximum tolerated dose
MUGA	multiple-gated acquisition
NCI	National Cancer Institute
NE	Not evaluable
NGS	Next Generation Sequencing
NOAEL	no-observed-adverse-effect level
NSCLC	non-small cell lung carcinoma
ORR	objective response rate
OS	overall survival

PD	progressive disease pharmacodynamic
PDGF	platelet-derived growth factor
PDGFRα/β	platelet-derived growth factor receptors alpha and beta
PET	positron emission tomography
PFS	progression free survival
PK	pharmacokinetic(s)
POPPK	population pharmacokinetics
PR	partial response
PRES	Posterior Reversible Encephalopathy Syndrome
PRO	patient-reported outcomes
PT	prothrombin time
PTT	partial thromboplastin time
QoL	quality of life
qPCR	quantitative polymerase chain reaction
QT_CF	QT interval corrected using Fridericia's method
RECIST	Response Evaluation Criteria in Solid Tumors, Version 1.1
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAS	statistical analysis software
SBP	systolic blood pressure
SD	stable disease
SOP	standard operating procedure
ß-hCG	human chorionic gonadotropin ß
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	elimination half-life
T3	triiodothyronine
T4	thyroxine
TMA	thrombotic microangiopathy
t_{max}	time to maximum concentration
TSH	thyroid stimulating hormone
UGT	uridine diphosphate-glucuronyltransferase
ULN	upper limit of normal
US	United States
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptors
V_{SS}/F	Volume of distribution at steady state
WBC	white blood cell

3 INTRODUCTION

3.1 Current standard of care for metastatic breast cancer

Metastatic breast cancer remains an incurable disease, with approximately 41,000 disease-associated deaths in the United States (US) annually [1]. Breast cancer includes three main molecular classes; i.e., estrogen receptor positive (ER+)/human epidermal growth factor receptor 2 (HER2)-negative breast cancers, HER2-overexpressing breast cancer, and triple negative breast cancers. ER+/HER2-negative phenotype is the most frequent and accounts for around 70% of all breast cancers. Endocrine therapy is the cornerstone treatment of ER+/HER2– metastatic breast cancer [2]. However, most of the patients will relapse after several months of treatment. Once endocrine resistant, prognosis is poor and patients with ER+/HER2– metastatic breast cancer are offered chemotherapy. For patients with HER2-overexpressing breast cancer, several therapies have been approved that meaningfully prolong progression free survival (PFS) and overall survival (OS) in these patients. With newer agents and combinations of existing agents, HER2-overexpressing breast cancer patients are experiencing profound and durable responses that can provide years of benefit. Lastly, those patients with triple negative breast cancer do not tend to respond to endocrine therapy or HER2-directed therapy. Therefore, these patients are generally offered chemotherapy with little hope for significant benefit. Although these three subtypes of metastatic breast cancer are treated with different drugs and have distinct prognoses, all of these patients will eventually develop resistance or intolerance to approved drugs. Therefore, there is a medical need for new pharmacological agents that improve outcomes for all patients with metastatic breast cancer.

3.2 Targeting FGF pathway metastatic breast cancer

The gene coding for fibroblast growth factor receptor 1 (FGFR1) is amplified in roughly 10% of breast cancers [3]. Several preclinical studies have suggested that targeting FGFR1 in *FGFR1*-amplified cell lines leads to antitumor effects. Shi et al [4] have shown that dovitinib (targeting FTL3, cKIT, FGFR, vascular endothelial growth factor receptor [VEGFR] 1, VEGF2, VEGF3, platelet-derived growth factor receptor [PDGFR], and CSF1R) inhibits *FGFR1*-amplified breast cancer cell lines, but not the *FGFR* non-amplified ones. Similar results were reported in another study showing that brivanib (VEGFR and FGFR1, 2 inhibitor) inhibits FGF-induced cell proliferation in *FGFR1*-amplified cell lines [5]. Furthermore, *FGFR1*-knock down was shown to decrease cell proliferation and reverse resistance to endocrine therapy in *FGFR1*-amplified breast cancer cell lines [6]. Currently, several FGFR inhibitors are being developed in the setting of metastatic breast cancer. One phase 2 trial has reported that dovitinib demonstrated anti-tumor activity in patients with *FGFR1*-amplified, but not in *FGFR1* non-amplified breast cancers [7].

In addition to *FGFR1* amplification, approximately 15% of breast cancers demonstrate amplification of an 11q (FGF3, FGF4, Cyclin D1, or FGF19) amplicon, and this change has been associated with poor prognosis [8]. This amplicon contains genes for FGF3, FGF4, and FGF19 proteins that are ligands of FGFR1. Amplification of that chromosome region (amplicon) may lead to increased signaling in the FGF/FGFR pathway, neo-angiogenesis, and mediation of resistance to targeted and endocrine therapies [9].

3.3 Targeting angiogenesis in metastatic breast cancer

It is well established that tumor growth beyond the size of 1–2 mm is angiogenesis-dependent [10]. The VEGF plays a central role in tumor angiogenesis. The biological functions of VEGF are mediated upon binding to receptor tyrosine kinases; VEGFR-1 (FLT-1), VEGFR-2, and VEGFR–3. VEGFRs are closely related to KIT and PDGFRs and are activated upon ligand-mediated receptor dimerization [11]. VEGF-inhibitors have shown activity in patients with metastatic breast cancer [12, 13]. Nevertheless, the magnitude of treatment efficacy is low and toxicity remains significant [14]. Based on these considerations, VEGF inhibitors are not considered as standard of care, although approved and reimbursed in several countries. Recent studies have suggested that FGFR-1 could play a critical role in tumor angiogenesis and tumor growth. FGFs are potent stimulators of angiogenesis in both normal and pathological tissues, having a direct effect on both vessel assembly and sprouting [15]. Blockade of the FGF pathway can overcome resistance to VEGFR inhibitors, emphasizing the importance of FGFR and specifically the need for multi-targeted inhibitors [16, 17].

3.4 Lucitanib for the treatment of FGF-aberrant metastatic breast cancer

Lucitanib is a selective orally available tyrosine kinase inhibitor targeting FGFR1–3, VEGFR1–3, and PDGFRα and β, with activity in relevant cell lines and animal models. Lucitanib is currently being developed by Clovis Oncology (in the US, and later Japan) and Les Laboratoires Servier (in Europe and elsewhere) for the treatment of patients with cancer. Considering the key roles of FGF and VEGF in the biology of metastatic breast cancer, selective inhibition of FGFR1–3, VEGFR1–3, and PDGFRα and β targets relevant pro-angiogenic growth factors, as well as simultaneously targeting proliferation and endocrine and/or anti-VEGFR therapy resistance in FGF-driven tumors.

3.5 Nonclinical Overview

3.5.1 Nonclinical pharmacology

3.5.1.1 Pharmacodynamics

Non-clinical pharmacology studies demonstrated significant anti-proliferative, anti-angiogenic, and anti-tumor activity of lucitanib. *In vitro,* lucitanib was a highly potent, selective inhibitor of the tyrosine kinase activity of FGFR1–3, VEGFR1–3, and PDGFRα/β [18]. In human cell line models, lucitanib inhibited the phosphorylation of VEGFR2, FGFR1, FGFR2, and PDGFRβ receptors and the proliferation of cancer cell lines dependent on FGFR1–3, VEGFR2, and PDGFRα receptor signaling for growth.

In vivo, the oral administration of lucitanib, over a range of well tolerated doses, to mice or rats significantly inhibited tumor growth in subcutaneous xenograft models using a range of human tumor cell lines or primary patient-derived tumors (breast, colon, ovarian, hepatocellular, renal, lung) [19, 20, 21, 22, 23, 24, 25, 26].

Lucitanib showed no significant inhibition when evaluated *in vitro* in a broad screen against receptors, ion channels, enzymes, and transporters suggesting that unexpected pharmacological activity is unlikely to be based on the concentration of inhibitor required for 50% inhibition (IC_{50}) obtained or on available tissue distribution data.

3.5.1.2 Safety pharmacology

Lucitanib, administered orally up to 80 mg/kg, is devoid of any notable effect on the central nervous system (CNS) and on the respiratory function in rat [27, 28].

In vitro, lucitanib had no effect on human ether-a-go-go-related gene (hERG) residual tail current, up to 10 µM [29]. *In vivo*, lucitanib increased blood pressure (BP) in rats and dogs and slightly decreased heart rate in dogs [30, 31, 32]. A complete recovery from the hypertensive effect occurred 2 days after treatment ended in rats. In dogs, all effects were reversible within 48 hours after treatment at a dose of 1 mg/kg/day, but were still present up to 72 hours after treatment at the higher doses (25 mg/kg). In dogs, there were no changes in QT corrected for changes in heart rate by Fridericia's formula. The dose of 1 mg/kg was the no-observed-adverse-effect-level (NOAEL) for cardiovascular variables in the dog. This dose corresponded to a mean C_{max} of 377 ng/mL.

3.5.2 Nonclinical pharmacokinetics and metabolism

Lucitanib pharmacokinetic (PK) properties were evaluated in nu/nu mice, Sprague Dawley rats, beagle dogs, and cynomologus monkeys. Concentrations of lucitanib in plasma were determined by protein precipitation followed by high performance liquid chromatography-tandem mass spectrometry [33, 34]. After oral administration, the absorption rate of lucitanib was moderate reaching time to maximum concentration (T_{max}) within 2–3 hours post-dosing [35, 36, 37, 38]. The absolute oral bioavailability was intermediate in rats and high in mice, dogs, and monkeys. Lucitanib was highly distributed in mice, rats, and monkeys, and in xenograft tumors implanted in nu/nu nude mice [39, 40]. Lucitanib is eliminated with a moderate clearance and a long half-life ($t_{1/2}$).

In humans, lucitanib is expected to be well absorbed; it showed high permeability in Caco-2 cell lines with minor impact of an efflux transporter [41]. Lucitanib is moderately metabolized by oxidative and conjugation routes. Recent results from *in vitro* metabolism studies indicated that lucitanib oxidative metabolism was mainly mediated by cytochrome P450 (CYP) isoforms 2C8 (~50%) and 3A4 (~50%). No potent inhibition of lucitanib on major human CYP isoforms was observed *in vitro* except for a possible non-competitive inhibition of CYP2B6 activity [42].

3.5.3 Toxicology

The toxicity of lucitanib was evaluated in rats and monkeys in repeat-dose studies with up to 28 days of dosing [43, 44] to support daily oral dose administration of lucitanib to cancer patients. The monkey was selected as the relevant non-rodent species for this toxicology program based on severe clinical signs of gastrointestinal (GI) toxicity, exposure variability in dogs. After daily oral administration over 4 weeks, the maximum tolerated dose (MTD) was 3.75 mg/kg in the rat and 2.5 mg/kg in the monkey. The rat was considered more sensitive than the monkey based on exposure at the MTD in both species.

The primary toxicological effects of lucitanib in both species were alterations in the hemolymphopoietic (HLP) system, kidneys, and skeletal system as well as circulatory disturbances (hemorrhages, angiectasis and/or vasculitis/vascular necrosis) in multiple organs/tissues (adrenal glands, GI tract, gall bladder [monkey only], bone marrow, brain choroid plexus [monkey only], skin, and liver). In addition, changes in the incisor teeth, ovaries, and male reproductive organs were noted in rats only. After a 2-week recovery

period, complete reversal of the effects was seen in squamous epithelium of the tongue, esophagus, and vagina in monkeys, and pancreas and ovaries in rats. Partial recovery was noted in the choroid plexus (monkeys), GI tract, liver, skin, exocrine glands, adipose tissue, and HLP system. Prominent changes were still present in the adrenal glands, kidneys, skeletal system, gall bladder (monkeys), male reproductive organs (rats), and teeth (rats).

Lucitanib was genotoxic and clastogenic in the three genotoxicity studies conducted.

3.6 Clinical Experience with Lucitanib

3.6.1 Clinical study #E-3810-I-01/CL1-80881-007

The ongoing first-in-human (FIH) clinical study with lucitanib (Study #E-3810-I-01) was initiated on 30 July 2010 at three clinical sites in Europe. The study is an open-label, dose-escalation, Phase 1/2 study to determine the MTD, recommended Phase 2 dose (RP2D), safety, efficacy, PK, and pharmacodynamics (PD) of lucitanib in adult patients with advanced solid tumors. The study consists of two phases, a dose-escalation phase followed by a dose-expansion phase at the identified RP2D [17, 45]. Patients are required to have histologically or cytologically confirmed locally advanced or metastatic solid tumors, relapsed or refractory to standard therapy. For the dose-expansion phase, patients were required to have tumors bearing *FGFR1* or *11q* 12–14 amplification (Cohort 1) or tumors sensitive to anti-angiogenic treatment (Cohort 2).

From July 2010 to September 2014, 134 patients were enrolled and 133 patients received at least one dose of lucitanib. The study is now closed to recruitment. Of the 133 patients, 24 patients had metastatic breast cancer.

3.6.1.1 Pharmacokinetics

The clinical PK properties of lucitanib were evaluated within the FIH study following single and multiple daily oral administrations. Lucitanib exposure exhibited high inter-patient variability. Lucitanib was rapidly absorbed with a maximum plasma concentration (C_{max}) reached within
1–3 hours. In the dose-escalation phase, exposure to lucitanib increased with increasing dose with no evidence of non-linearity. The $t_{1/2}$ of lucitanib was long (31–40 hours) and in agreement with the low apparent clearance and the moderate apparent volume of distribution. The moderate apparent volume of distribution is the result of high plasma protein binding limiting the distribution but a high permeability. At steady state, the area under the curve from time zero to 24 hours ($AUC_{0–24}$) was approximately double that on Day 1, consistent with daily administration of a compound with a $t_{1/2}$ of 31–40 hours.

3.6.1.2 Preliminary clinical efficacy

In the FIH study, heavily pre-treated patients were enrolled and demonstrated encouraging signs of activity. Specifically in dose-escalation: 3 out of 17 treated patients (with thymoma, small cell lung, and thymic epidermoid cancers) experienced durable stable disease (SD) lasting over 2.5 years: 40, 31, and 33 cycles, respectively.

During the dose-expansion phase, 21 patients were enrolled in the *FGF*-amplified cohort (Cohort 1); this cohort included 8 patients with *FGFR1*-amplified breast cancer and 4 patients with *11q*-amplified breast cancer. Seven of the 21 patients experienced a partial response (PR); 6 breast cancers (4 with *FGFR1*-amplified breast cancer and 2 with *11q*-amplified

breast cancer) and 1 bladder cancer. SD was confirmed in 12 patients (5 breast cancers, 2 renal cancers). Two patients experienced a best response of progressive disease (PD) (1 breast cancer, 1 squamous non-small cell lung carcinoma [NSCLC]). An additional non-evaluable breast cancer patient with extensive bone lesions had a clear metabolic response by positron emission tomography (PET) scan. PRs were seen in both hormone receptor positive and triple negative breast cancer patients. Most of the responses in the *FGF+* breast cohort were durable with a mean duration of response (DR) of 7.6 months. Importantly, there were responses in the 10, 15, and 20 mg starting dose levels and, upon dose reduction to 10 mg/day, the clinical benefit was maintained. The clinical efficacy of lucitanib was further demonstrated by a PFS of 9.4 months in this group of highly pre-treated advanced breast cancer patients. Two out of 3 patients with *FGFR1*-amplified squamous NSCLC experienced PD after two cycles; the third had SD for 8 months.

Five out of 24 patients in the anti-angiogenic sensitive continuous dosing cohort (Cohort 2) experienced a PR; in patients with thyroid (n = 2), hepatocellular, renal, and thymus cancers treated at 15 and 20 mg/day. These patients experienced a median DR of 7.3 months and a median PFS of 9.9 months. One patient who had advanced non-squamous NSCLC experienced a best response of PD. In the anti-angiogenic cohort, there were two breast cancer patients evaluated for tumor response; both patients had PD.

3.6.1.3 Summary of clinical safety

A combined interim safety analysis was performed inclusive of breast cancer patients enrolled to three Servier-sponsored clinical studies (CL1-80881-007, CL2-80881-001, CL1-80881-002), and 43 patients in this study (CO-3810-025) as of the data cutoff date of 21 May 2015. Across the ongoing lucitanib clinical studies of lucitanib in patients with metastatic breast cancer, patients were treated with one of six lucitanib doses, ranging between 5 mg and 30 mg daily administered on a continuous schedule or at 15 mg daily administered on two different intermittent schedules (5/2 or 21/7). A total of 230 patients administered at least one dose of lucitanib were included in the combined safety set. The most frequently reported treatment-emergent AEs are hypertension, asthenia, hypothyroidism, proteinuria, and anorexia; and GI disorders such as diarrhea, nausea, and vomiting. Most of these common (≥30%) AEs were assessed as Grade 1 or 2, except for hypertension, where the majority of subjects with a hypertension event had a Grade 3 event. A small number of patients had a Grade 4 event of hypertension. The AEs most commonly reported as related to study drug were similar to the most frequently reported AEs (≥30%), regardless of relationship to study drug or severity.

Approximately 40% of all patients had at least one SAE. Fourteen patients (6.1%) had an SAE of thrombotic microangiopathy; all were assessed by the Investigator as related to study drug, and 5 patients (2.3%) had an SAE of thrombotic microangiopathy that led to withdrawal of study drug. Although hypertension was reported in over 80% of all patients in the pooled analysis, and over 50% with a worst Grade 3, a comparatively low incidence of patients (2.6%) had a serious event of hypertension.

The most common AEs that led to discontinuation were hypertension and thrombotic microangiopathy (each 2.3%); for these, all were assessed as related to study drug.

Of the 230 patients in the pooled analysis, eight patients (3.5%) had an AE with a fatal outcome: disease progression and respiratory failure; general physical health deterioration,

tracheal haemorrhage; malignant neoplasm progression, and neoplasm progression. None of these fatal AEs were assessed as related to lucitanib.

One case of Posterior Reversible Encephalopathy Syndrome (PRES) also known as Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been reported in a 52-year-old female patient treated with lucitanib at the dose of 15 mg daily in Study #CL2-80881-001/BIG 2-13/FINESSE, sponsored by Institut de Recherches Internationales Servier. The diagnosis was confirmed by both the investigator and an external expert with the review of a follow-up MRI showing disappearance of the white matter lesions initially observed. This is the first diagnosed case of PRES related to lucitanib among approximately 242 patients treated with lucitanib to date. This type of event is therefore now recognized as an important potential risk of treatment with lucitanib.

It is described as a class-effect with anti-angiogenic molecules with a rare incidence of < 1%. However, several other risks factors have been described such as age, gender, exposure to hormone therapies (anti-estrogens) [46] and several chemotherapeutic agents or targeted therapies [47, 48, 49]. Clinical symptoms of PRES include confusion (71%), seizures (58%), headache (48%), visual disturbances (33%) or focal neurological deficit (10-15%) [48, 50]. These symptoms and signs are not specific and can be seen in many other neurological disorders. The clinical and radiological evolution of PRES is usually favorable, but the mortality is around 3-6 % and persistent neurological sequelae can be observed in 10-20% of cases [50].

The role of hypertension is discussed in several publications and it appears that pronounced fluctuations of BP, rather than absolute BP increase, might precede the syndrome. However, approximately 15-20% of patients with PRES are normotensive or hypotensive. Even among patients who are hypertensive, less than 50% have a documented mean arterial BP above the usually quoted upper limit of cerebral blood flow autoregulation (≥140-150mmHg) [50].

Precautionary measures are included in the protocol (Section 7.4.7)

The observed toxicity profile of lucitanib is related to its potent anti-VEGF activity and is consistent with those reported for other anti-angiogenic drugs. While lucitanib-associated AEs were reported by most patients, they rarely led to treatment discontinuations and when dose reductions were required, clinical activity was maintained. Although AEs were common, many patients enrolled in the FIH study (Study #E-3810-I-01) demonstrated meaningful clinical benefit from therapy. The tumor responses combined with the PD changes suggest that lucitanib is a clinically active drug in patients with solid tumors in both FGF-aberrant and anti-angiogenic cohorts.

3.7 Rationale for Study

This study will estimate PFS in patients with *FGFR1*- and 11q-amplifed, and non-amplified metastatic breast cancer. This endpoint is relevant to demonstrate not only the anti-tumor activity, but also the durability and tolerability of lucitanib in these patient populations.

Based on the phase 1/2, FIH study (Study #E-3810-I-01), 15 mg daily was advanced as the RP2D of lucitanib. However, interim data from ongoing lucitanib studies have shown that the daily dose of 15 mg is difficult for many patients to sustain and dose reductions have been frequently required. Further, clinical responses have been observed at both 10 mg and 15 mg daily dosing schedules. Therefore, in mid-2015, the decision was made to implement lucitanib at 10 mg daily across the clinical development program. In line with this change across the lucitanib clinical development program, enrollment to the 15 mg cohort (Cohort B)

has ended and enrollment to the 10 mg cohort (Cohort A) continues. Likewise, patients without *FGFR1* or 11q amplification (Cohort C) are to receive 10 mg of lucitanib daily.

This study will also evaluate the anti-tumor efficacy, safety, and population pharmacokinetic (POPPK)/PD relationships of oral single agent lucitanib, when administered to patients with *FGFR1*- or 11q-amplified and non-amplified breast cancer after failure of currently available standard therapies.

4 STUDY OBJECTIVES AND ENDPOINTS

4.1 Objectives

4.1.1 Primary Objective

- To estimate the anti-tumor efficacy of oral single-agent lucitanib as measured by investigator assessed PFS, when administered to patients with *FGFR1*- or 11q-amplified breast cancer after failure of currently available standard therapies

4.1.2 Secondary Objectives

- To estimate anti-tumor efficacy of oral single-agent lucitanib as measured by ORR, DR, disease control rate (DCR), and OS To estimate patient-reported outcomes (PRO) following treatment with lucitanib
- To evaluate safety and tolerability of lucitanib
- To assess the comparative PK of the lucitanib tablet formulation with the lucitanib capsule formulation

4.1.3 Exploratory Objectives

- To explore tumor tissue and blood-based biomarkers that may be predictive of response or primary resistance to treatment with lucitanib
- To explore blood-based PD biomarkers of lucitanib activity
- To determine PK of lucitanib in this patient population using population PK (POPPK) methods and explore correlations between exposure, response, and/or safety findings

4.2 Endpoints

4.2.1 Primary Endpoint

- PFS per RECIST Version 1.1 as determined by the investigator

4.2.2 Secondary Endpoints

- ORR according to RECIST Version 1.1
- DR and DCR according to RECIST Version 1.1
- OS
- Change from baseline in PRO using the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire
- Treatment emergent AEs, laboratory abnormalities, physical examinations including vital signs and electrocardiogram (ECG) abnormalities
- PK parameters including area under the concentration (AUC) curve from time zero to time t (AUC_{0-t}), C_{max}, T_{max}, $t_{1/2}$, volume of distribution at steady state (V_{SS}/F), and total plasma clearance (Cl/F) for lucitanib, if data allow

4.2.3 Exploratory Endpoints

- Concordance of tumor tissue *FGFR1* and 11q amplification assessed across different technical platforms (FISH, Next Generation Sequencing [NGS], comparative genomic hybridization [CGH], chromogenic in-situ hybridization [CISH], quantitative polymerase chain reaction [qPCR], or circulating tumor cells [CTCs/ctDNA]
- Exploration of different cut-off values for determining *FGFR1* and 11q amplification in tumor tissue by FISH and correlation with clinical efficacy
- Ribonucleic acid (RNA) expression of *FGFR1*, FGF3/4/19, and additional FGF family members; correlation with *FGFR1* and 11q amplification status and clinical efficacy
- Protein expression of *FGFR1* as determined by immunohistochemistry (IHC) in tumor tissue; correlation with *FGFR1* amplification status
- Genomic analysis of circulating tumor DNA (ctDNA)
- PD biomarker analysis measurement of circulating plasma biomarker levels including but not limited to FGF-2, FGF-23, sVEGFR1, VEGF-A, sCSF-1R, and CSF-1
- Pharmacogenomic analysis of variations in genes encoding proteins involved in absorption/distribution/metabolism/excretion (ADME)
- Plasma PK parameters for lucitanib based on sparse sampling for POPPK analysis

5 STUDY DESIGN

5.1 Overall Study Design and Plan

This is a phase 2, open-label, multicenter study evaluating the efficacy and safety of lucitanib administered orally to patients with metastatic breast cancer. Patients with *FGFR1*- or 11q (FGF3, FGF4, Cyclin D1, or FGF19)-amplified metastatic breast cancer may be enrolled into one of two different cohorts (Cohort A: FGF-amplified or Cohort C: FGF non-amplified, both receiving 10 mg daily).

For patients with local *FGFR1* or 11q test results, a central laboratory will confirm the presence or absence of the *FGFR1* and/or 11q amplification. Central testing prior to enrollment for these patients is not required for study enrollment.

Patients with local *FGFR1* and 11q results for whom the central reading does not confirm the amplification status can continue the study at the discretion of the investigator if clinical benefit is observed. If there are a significant number of patients with discordant local and central testing results, additional patients may be enrolled.

For patients without a local *FGFR1* or 11q test result, tissue may be submitted for central testing under a prescreening process, and a positive central laboratory test result is required for screening and subsequent enrollment of these patients.

FGFR1-amplified and 11q-amplified patients will be enrolled* as follows:

- Cohort A (10 mg): approximately 80 patients

FGF non-amplified patients will be enrolled as follows:

- Cohort C (10 mg): up to 40 patients

The dose assigned to patients enrolled into Cohort C depends on the version of the amendment approved at the time of patient enrollment (Amendment #3: 15 mg; Amendment #4: 10 mg).

*Amendment #4 removes the 1:1 randomized treatment assignment (10 mg vs. 15 mg) and accrual of patients to Cohort B (15 mg). Up to 80 patients were expected enrolled into Cohort B under the previous versions of this protocol.

Up to 20 patients enrolled will participate in a PK sub-study to assess the comparative PK of the lucitanib tablet formulation taken at Day –7 with the lucitanib capsule formulation taken at Day 1.

Patients in Cohorts A or C will be enrolled in the PK sub study at participating sites, as follows:

- Participation in the PK sub study will be optional for patients participating in Cohort A
- Participation in the PK sub study will be required for patients participating in Cohort C until enrollment of the PK sub study is completed

5.1.1 Screening Period

FGF-amplified (Cohort A) and FGF non-amplified (Cohort C) patients will undergo screening assessments within 28 days of the first dose of lucitanib.

Cohort A or C patients enrolled into the PK sub-study must undergo screening assessments within 21 days of the first dose of lucitanib, i.e., prior to Day –7.

For all patients, AEs will be assessed from the time of first dose of lucitanib through 28 days after the last protocol-specified treatment administration. Study-procedure-related AEs that occur after signing of the Informed Consent Form (ICF) and before administration of lucitanib will also be collected as AEs. AEs that occur after signing of the ICF and before lucitanib should be captured on the Medical History eCRF.

5.1.2 Treatment Period

Lucitanib will be administered once daily and swallowed with water (see Section 7.3). Patients should take lucitanib at approximately the same time each day, on an empty stomach, at least 2 hours before and 2 hours after a meal (fasting window is a total of four hours). Treatment with lucitanib is continuous but cycles will be defined as 28 days in duration. Dosing will be delayed or reduced according to protocol-specified toxicity criteria (See Section 7.4). Protocol-specified treatment will continue until there is clinical tumor progression or unacceptable toxicity.

Patients will undergo serial assessments for anti-tumor efficacy, drug safety, and PROs. Tumor scans will be acquired by the investigative site and evaluated locally for patient treatment decisions. Electronic copies of tumor scans will be uploaded to a central radiological vendor and held for review, if deemed necessary. Sparse blood sampling for POPPK analyses will be conducted in all patients treated with lucitanib. Serial blood sampling for PD evaluation will be conducted. Local laboratories will be used for standard hematology and chemistry tests. Echocardiogram (ECHO)/multiple-gated acquisition (MUGA) will be done locally. ECGs will be stored and may be analyzed centrally. Patients will be asked to self-monitor their BP at least two times per week and instructed to contact the study site in the event of a BP reading equal or above 160 mmHg systolic and/or greater than 100 mmHg diastolic (see Section 9.5.1.3).

Patients with SD or better after their Cycle 6 scan will continue to have tumor scans every 12 ± 1 weeks until tumor progression. After discontinuation of protocol-specified treatment, subsequent specific anticancer therapy used at the investigator's discretion will be recorded. Patients will be encouraged to undergo an optional post-treatment tumor biopsy at time of progression and before subsequent-line therapy is initiated.

5.1.3 End-of-Study

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

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

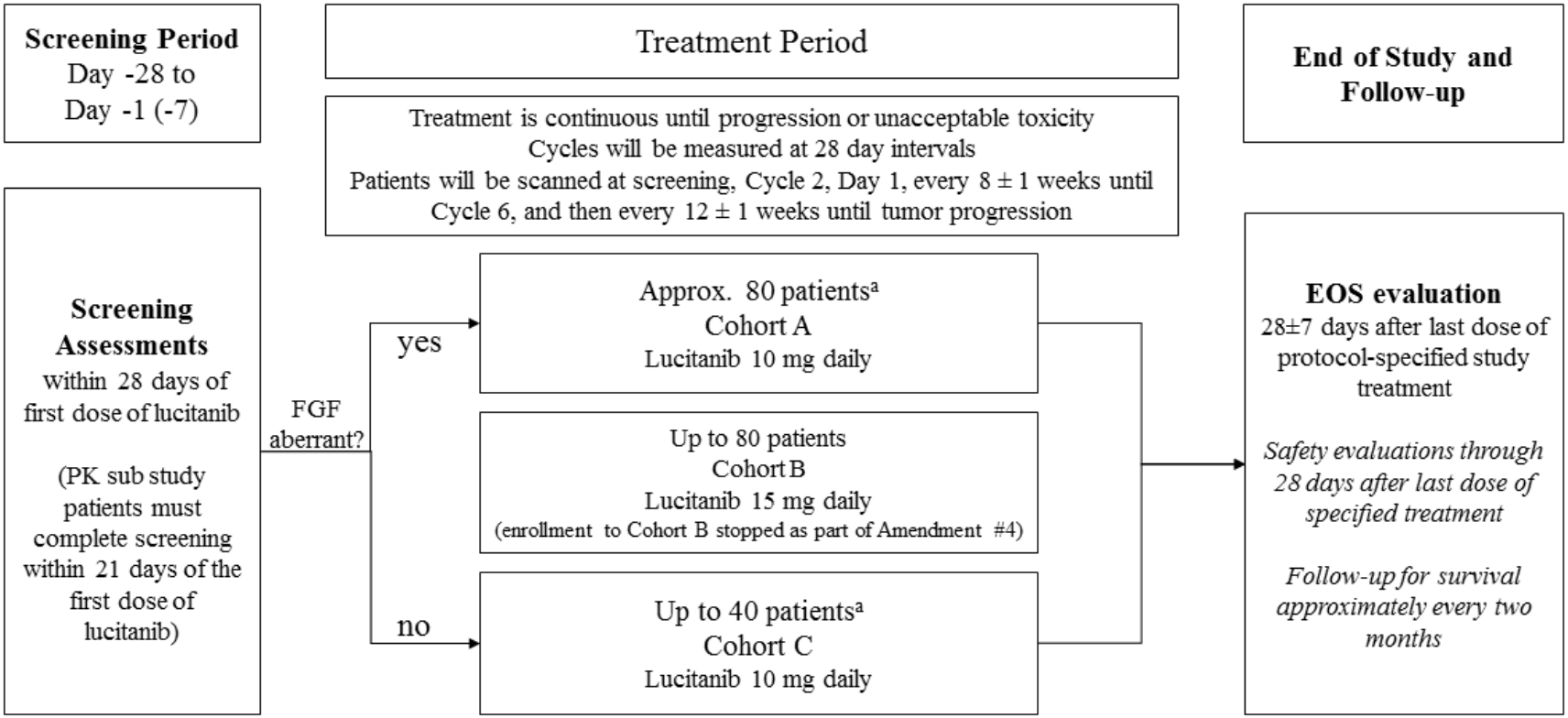
5.1.4 Long Term Follow-Up

All patients will be followed at approximately two monthly intervals to determine survival status, until death or sponsor decision to end the trial, whichever comes first.

5.2 Study Schema

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

Figure 1: Study Schema



[a] Up to 20 patients enrolled into Cohort C will participate in a PK sub study. Patients enrolled into Cohort A should also be considered for inclusion in the PK sub study at selected sites.

6 STUDY POPULATION

6.1 Number of Patients and Sites

FGFR1-amplified and 11q-amplified patients will be enrolled* as follows:

- Cohort A (10 mg): approximately 80 patients

FGF non- amplified patients will be enrolled into Cohort C as follows:

- Cohort C (10 mg): up to 40 patients

*1:1 randomization to Cohorts A and B was removed with Amendment #4.

Up to 20 patients will participate in a PK sub study to assess the comparative PK of the lucitanib tablet formulation with the lucitanib capsule formulation. Additional patients may be added to the PK sub-study to account for patients with incomplete PK sampling profiles at either Day –7 or Day 1, or to account for higher than expected variability in the observed PK profiles.

Enrollment into the PK sub study may only be opened at a limited number of sites based on study requirements and operational feasibility.

Patients in Cohorts A or C will be enrolled in the PK sub study at participating sites, as follows:

- Participation in the PK sub study will be optional for patients participating in Cohort A
- Participation in the PK sub study will be required for patients participating in Cohort C until enrollment of the PK sub study is completed

There will be approximately 30–40 investigative sites in the United States. All patients enrolled in Cohort C are required to participate in the PK sub study. Accrual to Cohort C will be limited to 10-15 sites participating in the PK sub study, until enrollment in the sub study has been filled.

6.2 Inclusion Criteria

All patients must meet all of the following inclusion criteria:

1. Histologically or cytologically confirmed metastatic breast cancer relapsed or refractory to approved standard available treatment
    - Specifically, patients with HER2-positive disease, as defined by the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines [51], must have exhausted approved HER2-directed therapies prior to enrollment
2. Prior treatment with standard first line therapy in the metastatic setting
3. *FGFR1* amplification or 11q amplification status determined on the most recent tumor tissue available, or detected in blood using validated methods for detecting circulating tumor cells (CTCs) or ctDNA:
    a) Patients in Cohort A: *FGFR1*- or 11q-amplified
    b) Patients in Cohort C: neither *FGFR1*- nor 11q-amplified

    Patient amplification status will be based on:

- local assessment by FISH, NGS, CGH, CISH, or qPCR; or
- local assessment in blood using validated methods for detecting circulating tumor cells (CTCs) or ctDNA; or
- central assessment by FISH, as confirmed by a prescreening process

4. Availability of formalin-fixed paraffin embedded (FFPE) tumor tissue sufficient for the central confirmation by FISH of *FGFR1* amplification or 11q amplification status. Detailed sample handling instructions are provided in the Laboratory Manual
5. Demonstrated progression of disease by radiological or clinical assessment
    - Measurable disease according to RECIST Version 1.1 is NOT required for enrollment
6. Patient, aged ≥18 years old
7. Eastern Cooperative Oncology group (ECOG) Performance status 0 or 1
8. Estimated life expectancy >6 months
9. Normal left ventricular function defined as a left ventricular ejection fraction (LVEF) ≥50% by ECHO or MUGA
10. Screening for laboratory values within the following parameters:
    - Hematology: absolute neutrophil count (ANC) ≥1000/mm^3; platelet count ≥100,000/mm^3; hemoglobin ≥9 g/dL
    - Renal function:
        - Serum creatinine <1.5 mg/dL or creatinine clearance >45 mL/min (Modification of Diet in Renal Disease formula [MDRD])
        - Dipstick protein measurement <2+. If dipstick ≥2+ then perform 24-hour urine protein measurements and if proteinuria <300 mg patient is eligible for inclusion
    - Liver function tests: total bilirubin ≤1.5 upper limit of normal (ULN; unless evidence of Gilbert's disease confirmed by uridine diphosphate-glucuronyltransferase [UGT] polymorphism); aspartate transaminase (AST) and alanine transaminase (ALT) ≤3 ULN; AST and ALT ≤5 ULN in case of liver metastases
11. For women with childbearing potential, a negative pregnancy test within 7 days prior to initiation of the study drug
12. Willingness to use an effective contraceptive method during the study and up to six months after the last dose is administered. Effective methods include the following: non-hormonal intrauterine device, barrier method (condoms, diaphragm) also in conjugation with spermicidal jelly, or total abstinence. Oral, injectable, or implant hormonal contraceptives are discouraged
13. Written consent on an Institutional Review Board (IRB)/Independent Ethics Committee(IEC)-approved ICF prior to any study-specific evaluation

6.3 Exclusion Criteria

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

1. Current or recent treatment with biologic anticancer therapies. Required washout for prior biologic anticancer therapies:
    - 3 months for bevacizumab
    - 28 days or five half-lives, whichever is shorter, for all other biologic therapies
2. Ongoing AEs from prior anticancer therapies, including radiation, targeted or cytotoxic therapies without resolution of any Grade 2 or greater side effects to Grade ≤1
3. Current treatment with any prohibited medications associated with prolongation of QT interval and known risk of Torsades de Pointes (see Appendix C)
4. Active CNS metastases, as indicated by clinical symptoms, cerebral edema, and/or progressive growth (patients with history of CNS metastases or cord compression are eligible if they are clinically stable for at least 4 weeks before first dose of lucitanib and do not require high-dose steroid treatment)
5. History of clinically significant or uncontrolled cardiac disease, including congestive heart failure (HF; New York Heart Association functional classification ≥3), angina, myocardial infarction within 6 months, or ventricular arrhythmia
6. QT_C prolongation (defined as a QT_C interval >470 msec according to Fridericia's correction)
7. Uncontrolled hypertension (defined as systolic blood pressure [SBP] ≥140 mmHg and/or diastolic blood pressure [DBP] ≥90 mmHg with optimized anti-hypertensive therapy)
    - The requirement for >2 anti-hypertensives to control hypertension at time of enrollment is exclusionary
8. Active second malignancy, i.e., patient known to have potentially fatal cancer present for which he/she may be (but is 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 (BMT) >2 years prior
9. Uncontrolled hypothyroidism defined as serum thyroid stimulating hormone (TSH) higher than 5 mIU/mL while receiving optimized thyroid hormone replacement therapy
10. Patient with history of thrombotic disorders:
    - Any history of venous thrombotic events, deep vein thrombosis (with the exception of catheter related deep vein thrombosis), or pulmonary embolism within 6 months prior to the first dose of lucitanib
    - Any history of arterial thrombotic events, cerebrovascular accident, or transient ischemic accident within 6 months prior to the first dose of lucitanib

- Any peripheral vascular disease or vasculitis which required treatment within 6 months prior the first dose of lucitanib
- Patient with hereditary risk factors of thromboembolic events (e.g., mutation of the Factor V of Leiden)

11. Received administration of strong inhibitors of CYP2C8 or CYP3A4 or strong inducers of CYP3A4 ≤7 days prior to first dose of lucitanib or have on-going requirements for these medications (Appendix E)
12. Received investigational treatment within 28 days prior to enrollment in this study
13. Non-study related minor surgical procedures ≤14 days prior to administration of lucitanib. In all cases, the patient must be sufficiently recovered and stable before treatment administration
14. History of major surgical procedure or significant trauma within 28 days prior to lucitanib. In all cases, the patient must be sufficiently recovered and stable before treatment administration
15. Females who are pregnant or breastfeeding
16. Presence of any serious or unstable concomitant systemic disorder incompatible with the clinical study (e.g., substance abuse, uncontrolled psychiatric condition, uncontrolled intercurrent illness including active infection, arterial thrombosis, and symptomatic pulmonary embolism)
17. Foreseeable poor compliance to the study procedures
18. 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, or become 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 7 days prior to administration of the first dose lucitanib. If the serum pregnancy results are not available prior to dosing, a urine pregnancy test can be performed to confirm that the patient is not pregnant prior to dosing. Both values should be entered in the electronic case report form (eCRF). Another serum pregnancy test will be performed at the end-of-study visit.

Patients of reproductive potential (males and females) must practice an effective method of contraception during treatment and for 6 months following the last dose of lucitanib. Adequate contraception is defined as double-barrier method (i.e., condom plus spermicide in combination with a diaphragm, cervical/vault cap, or intrauterine device). Oral, injectable, or implant hormonal contraceptives are discouraged.

Patients will be instructed to notify the investigator if pregnancy is discovered either during or within 6 months of completing treatment with lucitanib. This also applies to male patients whose

partners become pregnant while the patient is on study, or within the 6-month period after the last dose of lucitanib.

6.5 Waivers of Inclusion/Exclusion Criteria

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

7 DESCRIPTION OF STUDY TREATMENTS AND DOSE MODIFICATIONS

7.1 Description of Study Treatments

Lucitanib is supplied as an oral formulation as either hard gelatin capsules or tablets. A brief description of the investigational product is provided below (additional information may be found in the Investigator's Brochure and pharmacy manual):

Drug name:	CO-3810	
International Nonproprietary Name (INN):	lucitanib	
	Capsules	Tablets
Formulation:	2.5 mg (orange and white size 4), 5 mg (orange size 4), and 10 mg (white size 4)	5 mg (white), 7.5 mg (pink)
Excipients:	lactose monohydrate, sodium croscarmellose, and magnesium stearate	glycerol, pregelatinized starch, hydroxypropylmethyl cellulose, and magnesium stearate, polyethylene glycol 6000, titanium dioxide, iron oxide (7.5 mg only)
Temperature storage conditions:	59 – 77°F / 15 – 25°C	59 – 86°F / 15 – 30°C

Lucitanib is packaged in child-resistant tamper evident high-density polyethylene (HDPE) bottles. Bottles with capsules will contain desiccant.Lucitanib will be supplied to the study sites by the sponsor. Lucitanib supplies should be stored in their original packaging and not refrigerated. Each bottle of study drug will contain the unique identification code and the LOT number.

At the start of each cycle, the patient will receive sufficient lucitanib supplies to complete 4 weeks of treatment.

Bottles containing lucitanib will be labeled according to national regulations for investigational products. The expiry date will not appear on the labels, but will be controlled by the use of an Interactive Web Response System (IWRS).

7.2 Method of Assigning Patients to Treatment Groups

After confirming that patients fulfill entry criteria, the Investigator or his/her delegate will enroll patients as follows:

- Cohorts A and C (non-PK sub study patients): enrollment in IWRS on C1D1 to receive lucitanib at 10 mg daily*
- PK sub study patients: manual enrollment at Day -7 visit to receive single dose of 10 mg lucitanib in a tablet formulation, followed by enrollment in IWRS on C1D1 to receive lucitanib at 10 mg daily*

Based on analysis of data from the PK sub study and confirmation of acceptable PK comparability, patients may begin lucitanib treatment with the tablet formulation upon enrollment and patients who began treatment with capsule formulation may, at the discretion of the Sponsor and Investigator, be switched to the tablet formulation.

*Treatment should be initiated within 3 days of enrollment.

7.3 Preparation and Administration of Protocol-Specified Treatment

All patients will be assigned to receive lucitanib 10 mg daily. The treatment dose may be achieved by combining capsules or tablets of different strengths (see Section 7.1). Patients should take lucitanib as directed by the treating physician. Lucitanib should be taken with water (240 mL or 8 ounces). Patients should take lucitanib at approximately the same time each day, on an empty stomach, at least 2 hours before and 2 hours after a meal (fasting window is a total of four hours).

Treatment with lucitanib is continuous, but cycles will be defined as 28 days in duration. Dosing will be delayed or modified according to Dose Modification Criteria and Toxicity Management guidelines (See Section 7.4). Patients are allowed dose reductions by 2.5 mg increments after Cycle 1, Day 1 (C1D1).

Tablets and capsules must be transferred from the bottle to the mouth with minimal manipulations. The investigator will instruct the patient and personnel not to open the capsules; however, in the case of accidental release of the powder from the capsules, contaminated clothing should be removed and washed separately, rubber gloves should be put on, and all contaminated surfaces should be thoroughly cleaned with alcohol, a detergent solution, and then wiped clean with water. Patients should be advised to not suck, chew, or crush the capsules or tablets. Personnel should avoid exposure to crushed and/or broken tablets. In case of accidental skin contact with the content of the capsules or crushed tablets, the area should be flushed with large amounts of water for at least 15 minutes and then washed with soap. Contaminated material should be placed in an appropriate container and sealed before disposal.

If a patient misses a dose but is able to take it within six hours of the intended time, they should be instructed to take the missed dose, on an empty stomach as noted above. However, if the patient is not able to take the missed dose within six hours of the scheduled time, they should skip the missed dose and resume taking lucitanib at the normal time the following day. If a patient vomits the dose within 15 minutes of taking lucitanib, they should take an additional dose. If vomiting occurs more than 15 minutes after taking lucitanib, they should not take another dose until the normal time the following day.

Patients in the PK sub study that vomit after taking lucitanib on Day –7 or Day 1 should not take an additional dose of lucitanib, and PK sample collections should continue per protocol.

The investigator or designee will be responsible for distributing the appropriate strength(s) of lucitanib capsules to patients. A sufficient number of capsules 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 in a patient diary and will be instructed to bring their lucitanib capsules and diary to the next scheduled visit for reconciliation by site personnel.

7.4 Dose Modification Criteria and Toxicity Management

Patients are allowed dose reductions by 2.5 mg increments after C1D1 (with the exception of patients in the PK sub-study receiving lucitanib on Day –7 and Day 1). Patients are permitted to re-escalate at the start of a cycle by 2.5 mg as long as the cause of the dose reduction has resolved to Grade 1 or better. Dose escalations above 10 mg daily are not permitted.

7.4.1 Hypertension

As observed with other anti-angiogenic anti-cancer therapies, lucitanib can induce or exacerbate hypertension (as described in the Investigator's Brochure). Rapid increases in BP from pre-treatment measurements can be observed as early as the first few days following initiation of therapy. Hypertension can also occur later in the course of treatment.

Hypertension should be closely monitored and treated, if required. Abnormal BP measurements in clinic should be repeated within an hour to confirm findings.

Additionally, patients should be instructed to self-measure their BP at home at least two times per week while receiving lucitanib treatment. Patient-monitored BP should be followed by the investigator at all clinic visits to evaluate the effectiveness of anti-hypertensive treatment.

The early detection and effective management of hypertension are important to minimize risk for the patient and the need for lucitanib dose interruptions and reductions.

The following treatment and lucitanib dose adjustments algorithm should be followed in case hypertension is encountered:

Table 1: Hypertension Guidance Algorithm

Observation	Action
Patient experiences hypertension for the first time or patient with previously controlled hypertension experiences worsening in BP values with SBP from 140 to 159 mmHg and/or DBP from 90 to 99 mmHg.	**Patients without pre-existing hypertension**
	Initiate anti-hypertensive therapy immediately. Immediate use of two anti-hypertensive agents can be considered in case of rapid elevation of BP. The anti-hypertensive agent can be adjusted over a period of 14 days. The patient should be followed by the investigator at least once a week to evaluate the response to anti-hypertensive treatment. During this period, interruption of lucitanib or dose modification is not necessary. If BP decreases to < 140/90 mmHg within 14 days, continue lucitanib at the same dose.
	Patients with pre-existing hypertension
	Intensify/adapt any current anti-hypertensive treatment. Immediate dose and therapeutic class optimization should be performed. Up to three anti-hypertensive agents should be considered. The anti-hypertensive agent can be adjusted over a period of 14 days. The patient should be followed by the investigator at least once a week to evaluate the response to anti-hypertensive treatment. During this period, interruption of lucitanib or dose modification is not necessary. If BP decreases to < 140/90 mmHg within 14 days, continue lucitanib at the same dose.

Observation	Action
In case of persisting hypertension with SBP from 140 to 159 mmHg and/or DBP from 90 to 99 mmHg despite optimized anti-hypertensive treatment after 14 days.	Reduce lucitanib dose by 2.5 mg. Ensure adequate control of BP below 140/90 mmHg including increasing the dose of the current anti-hypertensive agent(s) (if appropriate) and/or initiation of additional anti-hypertensive agents, if required. Allow up to 14 days for BP to be controlled. If BP does not reduce to < 140/90 mmHg after 14 days, lucitanib should be reduced again by 2.5 mg (to the next lower dose). Allow an additional 14 days for BP to be controlled. If BP does not reduce to < 140/90 mmHg within the additional 14 days, lucitanib should be interrupted for up to 14 days. If BP decreases to < 140/90 mmHg within 14 days, restart lucitanib at the last dose. If BP remains at ≥ 140/90 mmHg after 14 days, sponsor approval is required prior to re-initiating lucitanib treatment.

Observation	Action
In case of confirmed hypertension with SBP equal or above 160 mmHg, and/or DBP equal or above 100 mmHg.	**Patients presenting no hypertension-related symptoms & no more than one risk factor[1]**
	Continue lucitanib therapy. Immediately start anti-hypertensive treatment or optimize current anti-hypertensive treatment. Allow up to 4 days for BP to be controlled (BP < 140/90 mmHg), with close follow-up by the treating physician. If BP does not reduce to ≤ 160/100 mmHg within 4 days, lucitanib should be reduced by 2.5 mg. If BP does not reduce to ≤ 160/100 mmHg within 4 additional days despite lucitanib dose reduction and optimal anti-hypertensive therapy, lucitanib should be interrupted. If BP decreases to < 140/90 mmHg within 14 days, resume lucitanib at next lower dose. If BP is not controlled < 140/90 mmHg) within 14 days after interruption of lucitanib and despite optimal anti-hypertensive treatment, lucitanib should be permanently discontinued.

Observation	Action
	Patients with mildly symptomatic hypertension[2] (outside of cardiovascular, cerebral, or major renal complications) or several risk factors[1] or already receiving two anti-hypertensive agents
	Temporarily interrupt lucitanib therapy. Immediate use of two anti-hypertensive agents may be considered in patients with no history of hypertension. For patients already on two anti-hypertensive agents, modification of the current anti-hypertensive therapy and/or adding a third agent should be considered. The patient should be followed by the investigator closely to evaluate the response to anti-hypertensive treatment. Allow up to 14 days for BP to be controlled (BP < 140/90 mmHg). If BP decreases to < 140/90 mmHg within 14 days, resume lucitanib at next lower dose. If BP does not reduce to < 140/90 mmHg within 14 days, lucitanib should be permanently discontinued.
In case of confirmed hypertensive crisis with life-threatening consequences. Hypertensive crisis is defined as an increase in BP (≥180 mmHg SBP and/or ≥120 mmHg DBP) that can lead to life-threating consequences (e.g., cerebral stroke).	Lucitanib must be permanently discontinued.

[1]Risk factors include those comorbidities that in the opinion of the investigator would increase the patient's risk of hypertension-related complications, e.g., diabetes, coronary artery disease
[2]Midly symptomatic hypertension defined as symptoms of headache, facial flushing, etc in the absence of additional cardiac or neurological findings

Pharmacological management should be based on the investigator's judgment and no definite recommendations for an anti-hypertensive agent can be made. However, calcium channel blockers may be preferred as initial treatment based on their rapidity of action and safety profile. Angiotensin Converting Enzyme (ACE) inhibitors can be considered in case of concomitant proteinuria [52, 53, 54]. In case of rapid elevation of BP, two anti-hypertensive agents should be

considered. The use of three anti-hypertensive agents, such as concomitant use of a renin-angiotensin system inhibitor, calcium channel blocker, and diuretic drug may be considered based on the investigator's decision. In that case, close surveillance of kidney function and electrolytes is strongly recommended.

Cardiologist and nephrologist advice should be sought when appropriate and especially in the context of associated AEs (i.e., proteinuria, as described below).

Sites should counsel patients on limiting salt intake to less than 4 g/day.

The patient must be educated before the first intake of lucitanib on the importance of BP self-monitoring, trained to recognize signs of hypertension, and to contact the site if BP is greater than 160/100 mmHg at any time.

For purposes of medical history reporting and AE reporting, it is important to strictly follow the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grading scale, taking into account not only the BP levels, but also the number of anti-hypertensive therapies.

After the withdrawal of lucitanib, the BP must continue to be monitored in order to adjust and progressively stop anti-hypertensive treatments that were started during the study (as appropriate).

Table 2: Grading scale for hypertension (NCI CTCAE Version 4.0)

Grade 1	Prehypertension (SBP 120–139 mmHg or DBP 80–89 mmHg)
Grade 2	Stage 1 hypertension (SBP 140–159 mmHg or DBP 90–99 mmHg); medical intervention indicated; recurrent or persistent (≥24 hours); symptomatic increase by >20 mmHg (DBP) or to >140/90 mmHg if previously within normal limits; monotherapy indicated
Grade 3	Stage 2 hypertension (SBP ≥160 mmHg or DBP ≥100 mmHg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated
Grade 4	Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated
Grade 5	Death

7.4.2 Proteinuria

Patients will be monitored for proteinuria by dipstick every two weeks during Cycle 1 and Cycle 2 and every 28 days thereafter. Patients with early signs of proteinuria by dipstick (2+) should be closely monitored and proteinuria evaluated quantitatively (24 hours protein excretion or protein-to-creatinine ratio). Additional safety monitoring should be performed as clinically indicated including tests for the assessment of free/conjugated bilirubin, haptoglobin N, schizocytes, or renal biopsy.

The following treatment and lucitanib dose adjustments algorithm should be followed in case proteinuria is encountered:

Table 3: Proteinuria Management Algorithm

In case of first onset of proteinuria ≥Grade 2 (i.e., ≥1 g in 24 hours by quantitative assessments)	Lucitanib treatment should be withheld and proteinuria monitored by dipstick twice weekly. Upon recovery of proteinuria to Grade ≤1 (1+ by dipstick or urinary protein <1.0 g/24 hours), lucitanib treatment should be resumed at the same dose and dipstick monitoring should continue
In case of second onset of proteinuria ≥Grade 2	Withhold the drug and perform a quantitative assessment of 24-hour urinary protein. Upon recovery, the lucitanib treatment should be resumed with a 2.5 mg dose reduction (e.g., 10 mg to 7.5 mg)
In case of third onset of proteinuria ≥Grade 2	Repeat assessments and dose modifications as outlined above (e.g., 7.5 mg to 5 mg)
In case of fourth onset of proteinuria ≥Grade 2	If proteinuria ≥ Grade 2 recurs following dose reductions to 5 mg, or if there is no recovery within 30 days, discontinue treatment permanently

In case of Grade 3 proteinuria or of additional risk factors (e.g., microhematuria, arterial hypertension), assessment of free/conjugated bilirubin, haptoglobin N, schistocytes, and/or renal biopsy may be indicated in consultation with a nephrologist.

Proteinuria will be graded as follows (CTCAE Version 4.0):

Grade 1: 1+ proteinuria; urinary protein < 1.0 g/24 hours

Grade 2: 2+ proteinuria; urinary protein ≥ 1.0–3.4 g/24 hours

Grade 3: Urinary protein ≥ 3.5 g/24 hours

7.4.3 Sub-clinical hypothyroidism

Plasma TSH and thyroid hormones levels should be measured, per protocol. Treatment with levothyroxine 50 µg/day is recommended for patients with TSH values above 5 mIU/L, even if triiodothyronine (T3) and thyroxine (T4) are normal. The treatment with lucitanib can continue at the same dose.

7.4.4 Decrease in LVEF

LVEF will be assessed by ECHO or MUGA. It is recommended to use the same technique for a given patient throughout the whole study duration. In case of HF symptoms or modification on imaging from baseline the following rules must be applied:

- No signs of HF and LVEF ≥45 % OR absolute drop from baseline ≤15 EF % points. Continue lucitanib at the same dose level and repeat LVEF assessment per protocol
- Patient is symptomatic OR LVEF <45% OR absolute drop from baseline >15 EF % points. Hold lucitanib until resolution (LVEF ≥50% and asymptomatic). If resolution occurs within 3 weeks, lucitanib can be resumed at a reduced dose by 2.5 mg increments, as described above, otherwise withdraw lucitanib permanently
- No recovery OR LVEF <20 %. Discontinue lucitanib permanently and follow-up the patient

7.4.5 QT_C prolongation

In case of CTCAE Grade 3 prolongation of the QT_CF (Fridericia correction) interval >500 msec, lucitanib treatment must be withheld.

Serum calcium, phosphorus, potassium, and magnesium levels should be analyzed, and levels should be corrected to within normal limits if needed. In all cases a second ECG must be carried out to confirm the QT_CF prolongation >500 msec within 1 hour of the initial ECG. A review of concomitant medications that could cause QT prolongation and/or Torsades de Points should be performed (see Section 8 and Appendix C).

Once QT_CF prolongation has resolved, lucitanib may be restarted at a 2.5 mg lower dose. Further dose reductions are permitted, as described above.

Grade 4 QT_C prolongation (QT_C >501 msec or >60 msec change from baseline and Torsades de Pointes or polymorphic ventricular tachycardia or symptoms of serious arrhythmia) should result in permanent discontinuation of lucitanib.

7.4.6 Liver function test abnormalities

In case of Grade 3 increase in ALT and AST, the dose will be withheld until recovery to Grade 2. If recovery occurs within 14 days, treatment will be resumed at the same dose level. If no recovery occurs within 14 days, the treatment will be resumed at a 2.5 mg lower dose upon recovery. Further dose reductions are permitted, as described above. In case of repeated events at 5 mg or absence of recovery to Grade 2 within 7 days, lucitanib will be stopped permanently.

In case of patient presenting with ALT >3 times the ULN concurrent with a total bilirubin >2 times the ULN with no evidence of hemolysis, and an alkaline phosphatase < 2 times the ULN or not available, lucitanib must be stopped permanently.

Abnormal values in AST and/or ALT concurrent with abnormal elevations in total bilirubin, in the absence of other causes of liver injury, are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and as such, should always be considered important medical events. Patients who present that combination of laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values.

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, physical assessment, and the possibility of hepatic neoplasia (metastases) should be considered. In addition to repeating AST and ALT, laboratory tests should include albumin, total bilirubin, direct bilirubin, prothrombin time (PT) and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, recreational drug and supplement consumption, family history, sexual history, travel history, history of contact with a jaundiced subject, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (e.g., biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the criteria mentioned above with no other cause for liver function test (LFT) abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs.

7.4.7 Management of Posterior Reversible Encephalopathy Syndrome (PRES)

If a patient presents with symptoms suggestive of PRES (e.g., persisting headache not responsive to usual analgesics, confusion, visual symptoms, seizures and coma), immediately interrupt lucitanib treatment and consider performing all relevant clinical and radiological examinations (e.g., neurological consultation, MRI) in order to ensure early diagnosis and treatment of this syndrome. A follow-up MRI should be performed in order to confirm the diagnosis of PRES, and if confirmed, lucitanib treatment must be permanently discontinued.

7.4.8 Other toxicities

For other Grade 3 or 4 hematologic and non-hematologic toxicities (except for alopecia), lucitanib treatment should be withheld until recovery to Grade 2 for hematological or Grade 1 for non-hematological toxicity. Upon recovery, the drug may be resumed at a 2.5 mg lower dose. Once the dose has been reduced within a treatment cycle, treatment continues at that dose level; no dose escalation is possible within a cycle. If a patient continues to experience toxicity after all allowed dose reduction steps as described above (i.e., after a patient has been dose-reduced from starting dose to 5 mg/day), or if dosing with lucitanib is interrupted for >14 consecutive days due to toxicity, treatment should be permanently discontinued, unless otherwise agreed between the investigator and the sponsor.

In the event of Grade 3 or 4 nausea and vomiting, antiemetics should be used. If, despite maximal antiemetic use, Grade 3 or 4 nausea or vomiting persists, lucitanib treatment should be withheld until recovery and dose reduction and discontinuation should follow the same paradigm as recommended for other Grade 3 and 4 non-hematologic toxicities.

7.4.9 Planned Surgery

In the case of planned surgeries, lucitanib should be temporarily withheld at least 7 days prior to and 7 days after a minor surgery (e.g., line placement, exploratory laparoscopy). Lucitanib should be temporarily withheld at least 14 days prior to and 14 days after a major surgery (e.g., bowel resection, cardiac bypass).

In all cases, lucitanib treatment should not be resumed until the surgical wound is fully healed.

7.5 Accountability of Protocol-Specified Treatment

Study personnel will maintain accurate records of lucitanib shipments/receipts, administration, and drug reconciliation. The study site is responsible for the return or destruction of lucitanib as required. With the exception of lucitanib bottles issued for the PK sub study, a drug management system (IWRS) will manage lucitanib inventory at all sites. Bottles of lucitanib for the PK sub study may be managed locally. For management of all other lucitanib requests and shipments, the IWRS is required. Any lucitanib accidentally or deliberately destroyed must be accounted for. All bottles must be accounted for prior to their destruction at the study center. Unused bottles should be destroyed locally. If destruction at the site is not possible, supply should be returned to the drug depot. During the course of the study and at completion of the study, the number of bottles of lucitanib 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 lucitanib.

7.7 Treatment Compliance

Documentation of dosing will be recorded in a study specific diary provided by the sponsor (or designee). 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 lucitanib taken at home in the diary and to bring the diary and all unused lucitanib supplies with them to scheduled clinic visits. A compliance check and lucitanib count will be performed by study personnel. Study site personnel will record compliance information in the eCRF and retain the diary in the patient's medical record.

Lucitanib will be permanently discontinued for patients that fail to take 14 or more doses due to non-compliance (not related to toxicity or planned surgery) within any two consecutive cycles, unless otherwise agreed between the investigator and the sponsor.

8 PRIOR AND CONCOMITANT THERAPIES

8.1.1 Permitted Concomitant Medication and Medications that Should be Used with Caution

All concomitant medications will be recorded in the eCRF. The following concomitant medications are permitted during the study or should be used with caution:

- Lucitanib is highly bound to plasma proteins; therefore, use caution with warfarin, which is also highly bound to plasma protein and has a narrow therapeutic window
- Supportive care (e.g., antiemetics, analgesics for pain control) may be used at the investigator's discretion and in accordance with institutional procedures
- Drugs with possible risk to cause prolonged QT interval and/or possible risk or conditional risk to cause Torsades de Pointes must be used with caution (see Appendix C)
- Transfusion of blood and blood products
- Treatment with antibiotics, anti-emetics, anti-diarrheals, analgesics, thyroid replacement therapy
- Bisphosphonates and denosumab in patients with bone metastases and for which the treatment was initiated prior to the initiation of study drug Considering the risk of drug-drug interactions, concomitant use of moderate inhibitors of CYP2C8 or CYP3A4 are not recommended during the study (see Appendix E)
- Any other medication as appropriate, except for prohibited medications as described in Section 8.1.2 below

8.1.2 Prohibited Concomitant Medications

The following concomitant medications are not permitted during the study:

- Systemic anticancer therapy (e.g., hormonal therapy, immune therapy, targeted therapy), except for bisphosphonates and denosumab in patients with bone metastases
- Prior treatment with bevacizumab within 3 months prior to the first dose of lucitanib
- Radiotherapy during the treatment period is prohibited. Palliative bone radiotherapy at focal sites can be allowed during the screening period, before lucitanib intake and providing recovery is achieved before study drug initiation
- Drugs known to cause prolonged QT interval and/or know risk of causing Torsades de Pointes (see Appendix C)
- Strong inhibitors of CYP2C8 or CYP3A4 are contraindicated during the study. Should acute treatment with a strong inhibitor be deemed necessary, lucitanib must be temporarily withheld. Lucitanib may be resumed after a minimum of seven days of ending acute treatment with a strong inhibitor of CYP2C8 or CYP3A4

- Co-administration of strong inducers of CYP3A4 (Appendix E) are not permitted at any time during treatment with lucitanib

9 STUDY PROCEDURES

Table 4 summarizes the procedures and assessments to be performed for patients in Cohorts A, B and C with exception of patients in the PK sub study; Table 5 summarizes the procedures and assessments to be performed for patients in the PK sub study.

Unless specified, all procedures and assessments are to be completed within ±2 days of the scheduled time point and are synchronized with administration day of lucitanib.

Table 4: Schedule of Assessments (All Cohorts)

		Treatment Period (Daily Dosing)[A]						
		Cycle 1			Cycle 2 and Beyond	Cycle 2 Only		
Procedure[B]	**Screening**	**Day 1[C]**	**Day 4**	**Day 15**	**Day 1**	**Day 15**	**End-of-Study**	**Two Monthly Follow-Up**
Informed Consent	X							
Medical/Oncology History	X							
Brief History			X	X		X		
Complete Physical Examination	X	X		X	X		X	
ECOG Performance Status	X	X			X		X	
Vital Signs, Height, Weight[D]	X	X	X	X	X	X	X	
Prior/Concomitant Medications and Procedures	X	X			X		X	
Contraceptive Counseling[E]	X						X	
Serum Pregnancy Test[F]	X						X	
Hematology, Including Reticulocytes[G]	X	X		X	X		X	
Serum Chemistry[H]	X	X		X	X		X	
Urinalysis[I]	X	X	X	X	X	X	X	
Tumor Scans (Including brain imaging for patients with known CNS metastases or when clinically indicated)[J]	X				X		X	
Submit FFPE Tumor Tissue[K]	X						X	
Adverse Events[L]	X	X	X	X	X	X	X	
Lucitanib Dispensation/Administration		X			X			
ECG Assessments[M]	X	X			X		X	
LVEF (ECHO or MUGA)[N]	X				X		X	
Plasma for ctDNA Analysis[O]	X	X		X	X		X	
Plasma PD Biomarker Sampling[P]	X	X		X	X		X	

		Treatment Period (Daily Dosing)[A]						
		Cycle 1			Cycle 2 and Beyond	Cycle 2 Only		
Procedure[B]	**Screening**	**Day 1[C]**	**Day 4**	**Day 15**	**Day 1**	**Day 15**	**End-of-Study**	**Two Monthly Follow-Up**
Blood for Sparse PK Sampling[Q]				X	X			
Pharmacogenomic Blood Sampling		X						
Quality of Life Questionnaire[R]		X			X		X	
Review and Collection of BP and Dosing Diary		X	X		X		X	
Survival Status							X	X
Subsequent Therapies for Breast Cancer							X	X

[A] Lucitanib will be administered daily, at least 2 hours before and 2 hours after a meal (on an empty stomach) with water (240 mL or 8 ounces). The total fasting period is 4 hours.

[B] Unless specified, procedure is completed ±2 days of scheduled time point. Procedures for C1D4 must be completed ±1 day of scheduled time point.

[C] Procedures required prior to lucitanib administration on C1D1 may be omitted if completed ≤3 days earlier during the screening period.

[D] Vital signs (BP, pulse, and temperature) taken pre-dose on drug administration days; height is only required once at screening. BP self-monitoring, two times per week, is requested from patients (see Section 9.5.1.3).

[E] Patients are to continue using effective contraception for 6 months after the last dose of lucitanib and report any pregnancies during this period.

[F] Serum ß-hCG (evaluated by local labs) will be performed only on women of childbearing potential ≤7 days prior to C1D1 and End-of-Study. 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, PT/PTT, and reticulocyte count ≤14 days prior to the first day of dosing. Blood will be sent for analysis at a local laboratory and must be reviewed by the investigator prior to start of lucitanib administration. Additional tests may be performed at the investigator's discretion.

[H] Includes TSH, T3, T4, total protein, albumin, creatinine, BUN or urea, total bilirubin, alkaline phosphatase, ALT, AST, glucose, sodium, potassium, chloride, CO_2, calcium, magnesium, and phosphorus, ≤28 days prior to first day of dosing. Total cholesterol will be completed during screening only. Blood will be sent for analysis at a local laboratory and must be reviewed by the investigator prior to start of lucitanib administration.

[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 C1D1, may be used as the baseline scans. Scans should preferably be CT scans of the chest, abdomen, and pelvis with intravenous contrast and appropriate slice thickness per RECIST Version 1.1, using the same methods throughout the study that were used to detect lesions at baseline. Other alternative studies (MRI, X-ray) may be performed if clinically indicated. Brain imaging is required at baseline and must be repeated at follow-up tumor assessments for patients with brain lesions. The first on-treatment scan should be completed on C2D1, and every 8 ± 1 weeks through Cycle 6 (i.e., C4D1, C6D1). Thereafter, scans should be completed every 12 ± 1 weeks (i.e., C9D1, C12D1, C15D1, etc.) until disease progression. Tumor scans do not need to be repeated at End-of-Study if <2 weeks since last scan or the patient had disease progression at the last scan. Scans will be evaluated locally for patient treatment decisions. Scans will be sent to a central radiological laboratory.

[K] For patient selection, *FGFR1* and 11q amplification status may be determined based on local assessment, or based on central assessment as confirmed by a prescreening process. FFPE tumor tissue is required for all enrolled patients. The post-treatment biopsy is optional and requires additional consent. Detailed sample handling instructions are provided in the Laboratory Manual.

[L] AEs will be assessed from the time of first dose of lucitanib through 28 days after the last dose.

[M] ECGs will be taken in triplicate anytime during screening, pre-dose (5–10 mins prior to dosing), and approximately 2 hrs (±5 mins) post-dose on Day 1 of each Cycle, and at End-of-Study, any time after treatment is discontinued.

[N] LVEF will be assessed by ECHO or MUGA. It is recommended to use the same technique for a given patient throughout the study. ECHO should be performed at Screening, on C2D1, and every 8 weeks thereafter, and at the End-of-Study.

[O] Whole blood will be collected pre-dose and processed locally for plasma ctDNA. Collections occur at screening, C1D1, C1D15, Day 1 of all subsequent Cycles, and End-of-Study. Refer to the Laboratory Manual for sample handling instructions.

[P] Whole blood will be collected pre-dose and processed locally for plasma for PD biomarkers. Refer to the Laboratory Manual for sample handling instructions.

[Q] Plasma levels for sparse PK of lucitanib will be measured on pre-dose samples collected on C1D15 and Day 1 of Cycles 2, 3, and 5. An additional sample will be collected on C2D1, 1–3 hours post-dose.

[R] Quality of Life Questionnaire (FACT-B) should be collected from the patient prior to dosing at C1D1; 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-Study.

Table 5: Schedule of Assessments (PK Sub Study)

	Screening		Treatment Period (Daily Dosing)[A]						
			Cycle 1			Cycle 2 and Beyond	Cycle 2 Only		
Procedure[B]	**Day –28 to Day –8**	**Day –7**	**Day 1[C]**	**Day 4**	**Day 15**	**Day 1**	**Day 15**	**End-of-Study**	**Two Monthly Follow-Up**
Informed Consent	X								
Medical/Oncology History	X								
Brief History				X	X		X		
Complete Physical Examination	X	X	X		X	X		X	
ECOG Performance Status	X	X	X			X		X	
Vital Signs, Height, Weight[D]	X	X	X	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		X	
Serum Chemistry[H]	X	X	X		X	X		X	
Urinalysis[I]	X	X	X	X	X	X	X	X	
Tumor Scans (Including brain imaging for patients with known CNS metastases or when clinically indicated)[J]	X					X		X	
Submit FFPE Tumor Tissue[K]	X							X	
Adverse Events[L]	X	X	X	X	X	X	X	X	
Single Dose Lucitanib Tablet Administration[M]		X							
Lucitanib Dispensation/Administration[M]			X			X			
ECG Assessments[N]	X	X	X			X		X	

	Screening		Treatment Period (Daily Dosing)[A]						
			Cycle 1			Cycle 2 and Beyond	Cycle 2 Only		
Procedure[B]	**Day –28 to Day –8**	**Day –7**	**Day 1[C]**	**Day 4**	**Day 15**	**Day 1**	**Day 15**	**End-of-Study**	**Two Monthly Follow-Up**
LVEF (ECHO or MUGA)[O]	X					X		X	
Plasma for ctDNA Analysis[P]	X		X		X	X		X	
Plasma PD Biomarker Sampling[Q]	X		X		X	X		X	
Blood for Sparse PK Sampling[R]					X	X			
Pharmacogenomic Blood Sampling			X						
Quality of Life Questionnaire[S]			X			X		X	
Review and Collection of BP and Dosing Diary		X	X	X		X		X	
Survival Status								X	X
Subsequent Therapies for Breast Cancer								X	X
Intensive PK Sampling[T]		X	X						

[A] Lucitanib will be administered daily, at least 2 hours before and 2 hours after a meal (on an empty stomach) with water (240 mL or 8 ounces). The total fasting period is 4 hours.

[B] Unless specified, procedure is completed ±2 days of scheduled time point. Procedures for C1D4 must be completed ±1 day of scheduled time point.

[C] Procedures required prior to lucitanib administration on C1D1 may be omitted if completed ≤3 days earlier during the screening period. The total time from the Day –7 visit to the Cycle 1 Day 1 visit must not be fewer than 7 days, but may be greater than 7 days, if necessary.

[D] Vital signs (BP, pulse, and temperature) taken pre-dose on drug administration days and post-dose following collection of the 24 hr PK samples on Day –7 and Day 1; height is only required once at screening. BP self-monitoring, two times per week, is requested from patients, including between Day –7 and Day 1 (see Section 9.5.1.3).

[E] Patients are to continue using effective contraception for 6 months after the last dose of lucitanib and report any pregnancies during this period.

[F] Serum ß-hCG (evaluated by local labs) will be performed only on women of childbearing potential ≤7 days prior to C1D1 and End-of-Study. 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, PT/PTT, and reticulocyte count ≤14 days prior to the first day of dosing. Blood will be sent for analysis at a local laboratory and must be reviewed by the investigator prior to start of lucitanib administration. Additional tests may be performed at the investigator's discretion.

[H] Includes TSH, T3, T4, total protein, albumin, creatinine, BUN or urea, total bilirubin, alkaline phosphatase, ALT, AST, glucose, sodium, magnesium, potassium, chloride, CO_2, calcium, and phosphorus ≤21 days prior to first day of dosing. Total cholesterol will be completed during screening only. Blood will be sent for analysis at a local laboratory and must be reviewed by the investigator prior to start of lucitanib administration.

[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 21 days prior to C1D1, may be used as the baseline scans. Scans should preferably be CT scans of the chest, abdomen, and pelvis with intravenous contrast and appropriate slice thickness per RECIST Version 1.1, using the same methods throughout the study that were used to detect lesions at baseline. Other alternative studies (MRI, X-ray) may be performed if clinically indicated. Brain imaging is required at baseline and must be repeated at follow-up tumor assessments for patients with brain lesions. The first on-treatment scan should be completed on C2D1, and every 8 ± 1 weeks through Cycle 6 (i.e., C4D1, C6D1). Thereafter, scans should be completed every 12 ± 1 weeks (i.e., C9D1, C12D1, C15D1, etc.) until disease progression. Tumor scans do not need to be repeated at End-of-Study if <2 weeks since last scan or the patient had disease progression at the last scan. Scans will be evaluated locally for patient treatment decisions. Scans will be sent to a central radiological laboratory.

[K] For patient selection, *FGFR1* and 11q amplification status may be determined based on local assessment, or based on central assessment as confirmed by a prescreening process. FFPE tumor tissue is required for all enrolled patients. The post-treatment biopsy is optional and requires additional consent. Detailed sample handling instructions are provided in the Laboratory Manual.

[L] AEs will be assessed from the time of first dose of lucitanib through 28 days after the last dose.

[M] On Day –7 a dose of the lucitanib tablet formulation will be given followed by a dose of the lucitanib capsule formulation on Day 1.

[N] ECGs will be taken in triplicate anytime during screening, pre-dose (5–10 mins prior to dosing), and approximately 2 hr (±5 min) post-dose on Day –7 (Cohort C) and Day 1 (All Cohorts) of each Cycle, and at End-of-Study, any time after treatment is discontinued.

[O] LVEF will be assessed by ECHO or MUGA. It is recommended to use the same technique for a given patient throughout the study. ECHO should be performed at Screening, on C2D1, and every 8 weeks thereafter, and at the End-of-Study.

[P] Whole blood will be collected pre-dose and processed locally for plasma ctDNA. Collections occur at screening, C1D1, C1D15, Day 1 of all subsequent Cycles, and End-of-Study. Refer to the Laboratory Manual for sample handling instructions.

[Q] Whole blood will be collected pre-dose and processed locally for plasma for PD biomarkers. Refer to the Laboratory Manual for sample handling instructions.

[R] Plasma levels for sparse PK of lucitanib will be measured on pre-dose samples collected on C1D15 and Day 1 of Cycles 2, 3, and 5. An additional sample will be collected on C2D1, 1–3 hours post-dose.

[S] Quality of Life Questionnaire (FACT-B) should be collected from the patient prior to dosing at C1D1; 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-Study.

[T] PK specimens will be collected at the following time points on Day –7 and Day 1: 5–10 min pre-dose, post-dose at 15 (±2) min, 30 (±3) min, 1 hr (±5 min), 1.5 hr (±5 min), 2.5 hr (±10 min), 4 hr (±15 min), 6 hr (±15 min), 8 hr (±15 min), 10 hr (±30 min) (optional), and 24 hr (±30 min).

9.1 Screening Period

Following written informed consent, and unless otherwise specified, the following assessments should be performed during the 28-day period prior to the first dose of lucitanib. Assessments performed prior to patient signing informed consent are acceptable only if confirmed to have been standard of care.

Up to 20 patients enrolled in Cohort A and Cohort C will participate in a PK sub study at select sites. These patients should have all screening assessments performed within the 21-day period prior to the first dose of lucitanib, i.e., between Day –28 and Day –8 (Table 5).

- Medical history, including demographic information (birth date, race, gender, etc.), smoking status, and oncology history including date of cancer diagnosis, prior cancer treatment, and any surgical procedures
- Documentation of tumor tissue results demonstrating *FGFR1* or 11q amplification (Cohorts A and B) or *FGFR1* and 11q non-amplification (Cohort C) by established laboratory methods (e.g., FISH, NGS, CGH, CISH, or qPCR); or local assessment in blood using validated methods for detecting CTCs or ctDNA
  - For patients without local test results of *FGFR1* or 11q amplification, or *FGFR1* and 11q non-amplification, a separate prescreening consent will be available to enable testing before initiating additional CO-3810-025 specific screening. Patients must read and sign a separate prescreening consent form to undergo testing of tissue by the central laboratory. Upon central confirmation of *FGFR1* or 11q amplification, or *FGFR1* and 11q non-amplification, patients may consent for and begin screening for the study.
- Complete physical examination by body system, height, and weight
- ECOG performance status
- Vital signs (BP, pulse, and temperature)
- Prior and concomitant medications and procedures
- Contraceptive counseling
- Serum pregnancy test (by local laboratory) ≤7 days prior to the first day of dosing for women of childbearing potential. If the serum pregnancy test results are not available prior to dosing, a urine pregnancy test can be performed to confirm that the patient is not pregnant prior to dosing. Both values should be entered in the eCRF
- Hematology (hemoglobin, hematocrit, white blood cell [WBC] and differential [with ANC], platelet count, PT/partial thromboplastin time (PTT), and reticulocyte count) ≤14 days prior to the first day of dosing
- Serum chemistry (TSH, T3, T4, total protein, albumin, creatinine, blood urea nitrogen [BUN] or urea, total bilirubin, alkaline phosphatase, ALT, AST, glucose, sodium, potassium, chloride, CO_2, calcium, magnesium, phosphorus, and total cholesterol)

- 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. Assessments should consist of clinical examination and computed tomography (CT) scans of the chest, abdomen, and pelvis with intravenous contrast and appropriate slice thickness per RECIST Version 1.1; other alternative studies (magnetic resonance imaging [MRI] and X-ray) may be performed if clinically indicated. The same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study
- Brain imaging is required at baseline. Patients with brain lesions detected at baseline require 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
- Archival FFPE tumor specimen for central laboratory confirmation of *FGFR1* or 11q amplification status and companion diagnostic development is required. Detailed sample handling instructions are provided in the Laboratory Manual
- Blood sampling for ctDNA analysis. Detailed sample handling instructions are provided in the Laboratory Manual
- Blood sampling for biomarker analysis. Detailed sample handling instructions are provided in the Laboratory Manual
- 12-lead ECG (in triplicate, 10-sec tracings >2 min apart)
- LVEF (ECHO or MUGA)

At the end of screening, patients may be enrolled to receive daily treatment with lucitanib 10 mg (see Section 7.2).

9.2 Treatment Period

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

Patients will receive lucitanib 10 mg daily. Beginning on Day 1, lucitanib will be administered once daily to be swallowed with water (240 mL or 8 ounces). Patients should take lucitanib at approximately the same time each day, on an empty stomach, at least 2 hours before and 2 hours after a meal. Patients will record the dose and timing of administration of oral lucitanib in their daily dosing diary. Treatment with lucitanib is continuous but cycles will be defined as 28 days in duration.

BP self-monitoring should be completed at least twice a week by patients and measurements should be recorded in their diaries and brought to the clinic visits for review (see Section 9.5.1.3).

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

9.2.1 Day –7 PK Sub Study

The following pre-dose and post-dose assessments will be performed at Day –7 for patients participating in the PK sub study:

Pre-dose Assessments	Post-dose Assessments
• Complete physical examination • Weight • ECOG performance status • Vital signs (BP, pulse, and temperature) • Concomitant medications • Hematology (including reticulocyte count) and serum chemistry • Urinalysis • AE monitoring • 12-lead ECG (in triplicate, 10-sec tracings >2 min apart) 5–10 min prior to dosing • PK blood sample (5–10 min prior to dosing)	• 12-lead ECG (in triplicate, 10-sec tracings >2 min apart), 2 hours (±5 min) following dosing with lucitanib • AEs experienced by the patient since dosing will be documented • Concomitant medications administered since dosing will be recorded • PK blood sampling collected at the following time points: 15 (±2) min, 30 (±3) min, 1 hr (±5 min), 1.5 hr (±5 min), 2.5 hr (±10 min), 4 hr (±15 min), 6 hr (±15 min), 8 hr (±15 min), 10 hr (±30 min) (optional), and 24 hr (±30 min) • Vital signs (BP, pulse, and temperature) taken after last PK sample

9.2.2 Day 1 of Cycle 1 (C1D1:PK sub study patients)

The following procedures will be performed at C1D1 for patients participating in the PK sub study:

Pre-dose Assessments	Post-dose Assessments
• Complete physical examination • Weight • ECOG Performance status • Vital signs (BP, pulse, and temperature) • Concomitant medications • Hematology (including reticulocyte count) and serum chemistry • Urinalysis • Blood sampling for ctDNA analysis • Blood sampling for biomarker analysis • Blood sampling for pharmacogenomics analysis • AE monitoring • Lucitanib will be dispensed to the patient • 12-lead ECG (in triplicate, 10-sec tracings >2 min apart) 5–10 min prior to dosing • QoL Questionnaire (FACT-B) • PK blood sample (5–10 min prior to dosing)	• 12-lead ECG (in triplicate, 10-sec tracings >2 min apart), 2 hours (±5 min) following dosing with lucitanib • AEs experienced by the patient since dosing will be documented • Concomitant medications administered since dosing will be recorded • PK blood sampling collected at the following time points: 15 (±2) min, 30 (±3) min, 1 hr (±5 min), 1.5 hr (±5 min), 2.5 hr (±10 min), 4 hr (±15 min), 6 hr (±15 min), 8 hr (±15 min), 10 hr (±30 min) (optional), and 24 hr (±30 min) • Vital signs (BP, pulse, and temperature) after last PK sample

9.2.3 Day 1 of Cycle 1 (C1D1; all patients with exception of PK sub study)

Patients will be required to take their first dose of lucitanib at the clinic and within 3 days of enrollment. The following procedures will be performed on C1D1 for all patients with exception of those in the PK sub study:

Pre-dose Assessments	Post-dose Assessments
• Complete physical examination • Weight • ECOG performance status • Vital signs (BP, pulse, and temperature) • Concomitant medications • Hematology (including reticulocyte count) and serum chemistry • Urinalysis • Blood sampling for ctDNA analysis • Blood sampling for biomarker analysis • Blood sampling for pharmacogenomics analysis • AE monitoring • Lucitanib will be dispensed to the patient • 12-lead ECG (in triplicate, 10-sec tracings >2 min apart) 5–10 mins prior to dosing • Quality of Life (QoL) Questionnaire (FACT-B)	• 12-lead ECG (in triplicate, 10-sec tracings >2 min apart), 2 hours (±5 min) following dosing with lucitanib • AEs experienced by the patient since dosing will be documented • Concomitant medications administered since dosing will be recorded •

9.2.4 Day 4 of Cycle 1 (C1D4; all patients)

The following procedures will be performed during the visit.

Assessments
• Brief history and review of AEs • Weight • Vital signs (BP, pulse, and temperature) • Urinalysis • AE monitoring • Review and collection of BP diary

9.2.5 Day 15 of Cycle 1 (C1D15; all patients)

The following procedures will be performed during the visit. Patients will be instructed to refrain from taking their dose of lucitanib at home on the day of their clinic visit.

Assessments
• Brief history and complete physical examination • Weight • Vital signs (BP, pulse, and temperature) • Hematology (including reticulocyte count) and serum chemistry • Urinalysis • AE monitoring • Pre-dose blood sampling for ctDNA analysis • Pre-dose blood sampling for PD analysis • Pre-dose blood for sparse PK sampling

9.2.6 Day 1 of Cycle 2 (C2D1) and Subsequent Cycles (all patients)

Patients will be instructed to refrain from taking their dose of lucitanib at home on the day of their clinic visit because the dose will be taken during the clinic visit.

The following procedures will be performed pre-dose and post-dose at C2D1 and subsequent visits:

Pre-dose Assessments	Post-dose Assessments
• Complete physical examination • Weight • ECOG performance status • Vital signs (BP, pulse, and temperature) • Concomitant medication since last visit • Hematology (including reticulocyte count) and serum chemistry • Urinalysis • Blood sampling for ctDNA analysis • Blood sampling for biomarker analysis • AE monitoring • 12-lead ECG (in triplicate, 10-sec tracings >2 min apart) 5–10 mins prior to dosing • LVEF (ECHO or MUGA) – every 8 weeks post-C2D1 • Blood for sparse PK sampling (Day 1 of Cycles 2, 3, and 5) • QoL Questionnaire (FACT-B) 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.) • Lucitanib will be dispensed to the patient	• 12-lead ECG (in triplicate, 10-sec tracings >2 min apart), 2 hours (±5 min) following dosing with lucitanib • AEs experienced by the patient since dosing will be documented • Concomitant medications administered since dosing will be recorded • PK sample 1–3 hours post-dose on Day 1 of Cycle 2

Other assessments required during the visit and irrespective of dosing are:

- Tumor assessments will be performed at Cycle 2, Day 1 and thereafter every 8 ± 1 weeks until Cycle 6 and thereafter every 12 ± 1 weeks until tumor progression (see Section 9.5.2.1)
- Review and Collection of BP and dosing diary

9.2.7 Day 15 of Cycle 2 (C2D15; all patients)

The following procedures will be performed during the visit.

Assessments
• Brief history and review of AEs • Weight • Vital signs (BP, pulse, and temperature) • Urinalysis • AE monitoring

9.3 End-of-Study Visit (all patients)

The following procedures will be performed for all patients 28 days (±7 days) after the last dose of protocol-specified treatment:

- Complete physical examination
- Weight
- ECOG performance status
- Vital signs (BP, pulse, and temperature)
- Concomitant medications since last visit
- Contraceptive counseling
- Serum pregnancy test for women of childbearing potential
- Hematology (including reticulocyte count), and serum chemistry
- Urinalysis
- Tumor scans (using the same methodology as was used at screening), including brain scans for patients with brain lesions at baseline, unless it has been <2 weeks since last scan or disease progression was noted on the last scan
- Blood sampling for ctDNA analysis
- Blood sampling for biomarker analysis
- AE monitoring (until 28 days after last dose of protocol-specified treatment; all ongoing SAEs should be followed until resolution or stabilization. After the 28-day window, only new SAEs assessed as related to study drug should be recorded)
- Review and collection of BP and dosing diary
- 12-lead ECG (in triplicate, 10-sec tracings >2 min apart)

- LVEF (ECHO or MUGA)
- QoL questionnaire (FACT-B)
- Survival status
- Subsequent therapies for breast cancer
- Optional post-treatment biopsy for PD analyses, at time of disease progression and before subsequent anti-line therapy is initiated

9.4 Two Monthly Follow-Up (All Cohorts)

- Survival status
- Subsequent therapies for breast cancer

9.5 Methods of Data Collection

9.5.1 Safety Evaluations

9.5.1.1 Adverse Event Assessment

The investigator has the responsibility for assessing the safety of the patients and for compliance with the protocol to ensure study integrity. Patients will be monitored for AEs from the time of first dose of lucitanib through 28 days after the last dose of protocol-specified treatment. Study-procedure-related AEs that occur after signing of the ICF and before administration of lucitanib will also be collected. Any ongoing SAEs will be followed until resolution or stabilization. AEs and laboratory abnormalities will be graded according to the NCI CTCAE Version 4.03 [55] grading system and recorded in the eCRF.

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

9.5.1.2 Clinical Laboratory Investigations

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), platelet count, PT/PTT, and reticulocyte count per the schedule of evaluation at screening, during treatment, and at the end-of-study visit. Hematology results must be reviewed by the investigator prior to the start of treatment with lucitanib.

Clinical Chemistry: TSH, T3, T4, total protein, albumin, creatinine, BUN or urea, total bilirubin, alkaline phosphatase, ALT, AST, glucose, sodium, potassium, chloride, CO_2, calcium, magnesium, and phosphorus per the schedule of evaluations at screening, during treatment, and at the end-of-study visit. Total cholesterol will be performed at screening only.

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, during treatment, and at the end-of-study visit.

Serum Human Chorionic Gonadotropin ß (ß-hCG) Pregnancy Test: Performed on women of childbearing potential ≤7 days prior to administration of the first dose of lucitanib, and at the end-of-study visit. If the serum pregnancy test results are not available prior to the first dose of lucitanib, a urine pregnancy test can be performed 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 lucitanib can be administered.

Laboratory reports will be reviewed by the investigator or delegated physician to assess clinical significance. Clinically significant abnormalities should be documented in the eCRF as an AE as defined in Section 10.4.

9.5.1.3 Vital Signs

Vital signs will include BP, 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-study visit.

BP self-monitoring should be completed at least twice a week by patients and measurements should be recorded in their diaries and brought to the clinic visits for review. For the week following the first dose of lucitanib, patients are encouraged to record BP in their diary at least once, but preferably twice, prior to their C1D4 visit. After review, the investigator will consider whether the readings require medical treatment or reporting as an AE. Patients are instructed to contact the investigator, if BP values equal or above 160 mmHg systolic and/or equal or above 100 mmHg diastolic. Equipment and guidance to the patients on how to self-monitor their BP will be provided by the sponsor.

9.5.1.4 12-Lead Electrocardiograms

Serial 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:

<u>All cohorts:</u>

- Screening: anytime during the screening period
- Day 1 of each treatment cycle: Pre-dose (5–10 minutes prior to dosing) and 2 hours (± 5 min) following dosing with lucitanib
- End-of-Study: Any time after dosing has been discontinued, but within 28 days of last dose

PK Sub Study:

- Day –7: Pre-dose (5–10 minutes prior to dosing) and 2 hours (± 5 min) after dosing with the lucitanib tablet formulation

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

9.5.1.5 LVEF

LVEF will be assessed by ECHO or MUGA at screening, on Day 1 of Cycle 2 and every 8 weeks thereafter, and at the End-of-Study. It is recommended to use the same technique for a given patient throughout the whole study duration. ECHO/MUGA results will be analyzed locally.

9.5.1.6 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).

9.5.1.7 Physical Examinations

Physical examinations will include an assessment of all the major body systems. Complete physical examinations will be performed at screening, Day –7 (PK sub study only), Day 1 of each cycle, C1D15, Day 1 of each cycle, and at the end-of-study visit.

9.5.1.8 ECOG Performance Status

ECOG performance status (Appendix B) will be assessed at screening, Day –7 (for patients participating in the PK sub study only), and on Day 1 of each cycle during treatment, and at the end-of-study visit. ECOG performance status should be assessed by the same study personnel at each visit, if possible. Care will be taken to accurately score performance status, especially during screening for study eligibility purposes. Additional consideration should be given to borderline ECOG performance status to avoid enrolling patients with significant impairment.

9.5.2 Efficacy Evaluations

9.5.2.1 Tumor Assessments

The first on-treatment scan should be completed on Cycle 2, Day 1, and every 8 ± 1 weeks through Cycle 6 (i.e., C4D1, C6D1). Thereafter, scans should be completed every 12 ± 1 weeks (i.e., C9D1, C12D1, C15D1, etc.) until disease progression. All patients must have scans to confirm radiographic progression. Tumor scans do not need to be repeated at end-of-study if <2 weeks since last scan or the patient had disease progression at the last scan. Patients that permanently discontinue lucitanib should continue scans until radiographic disease progression. Scans will be evaluated locally for patient treatment decisions. Copies of tumor scans will be

collected centrally to facilitate independent evaluation if subsequently required. Tumor response will be interpreted using RECIST Version 1.1 (Appendix A).

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

Brain imaging is required at baseline. Patients with brain lesions detected at baseline require 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 lesions throughout the clinical study.

9.5.3 Biomarker Assessments

The following biomarker assessments will be done:

- *FGFR1* and 11q amplification status in tumor tissue assessed by FISH, CISH, NGS, and qPCR
- RNA expression of various genes related to signaling pathways inhibited by lucitanib including, but not limited to FGFR1, FGF3/4/19, and additional FGF family members
- Protein expression of FGFR1 as determined by IHC

FFPE tumor tissue will be used for *FGFR1* and/or 11q amplification confirmatory central laboratory testing. Detailed sample handling instructions are provided in the Laboratory Manual. Tumor samples may be used to develop a tissue-based diagnostic test.

Following disease progression, patients will be encouraged to undergo an optional post-treatment tumor biopsy before subsequent-line therapy is initiated.

Sample handling instructions will be provided in a separate Laboratory Manual.

9.5.4 Population PK Assessments

Plasma levels of lucitanib will be measured on pre-dose samples collected on Day 15 of Cycle 1 and Day 1 of Cycles 2, 3, and 5. An additional sample will be collected on Cycle 2, Day 1, 1–3 hours post-dose. Sparse blood sampling for POPPK analyses will be conducted in all patients treated with lucitanib. Refer to the Laboratory Manual for sample handling instructions.

9.5.5 PK Sub Study

Up to 20 patients will participate in the PK sub study. PK sampling will be performed at specified time points on each on the following two days:

- Day –7: lucitanib in tablet formulation
- Day 1: lucitanib in capsule formulation

The dose assigned for patients participating in the PK sub study will be the same for Days –7 and 1 and depends on the version of the amendment approved at the time of patient enrollment (Amendment #3: 15 mg; Amendment #4: 10 mg).

The total time from the Day -7 visit to the Cycle 1 Day 1 visit must not be fewer than 7 days, but may be greater than 7 days, if necessary. Lucitanib will not be taken between Day -7 and Cycle 1, Day 1.

PK specimens will be taken on Day –7 and Day 1 PK specimens will be collected 5–10 min pre-dose, and post-dose at 15 (±2) min, 30 (±3) min, 1 hr (±5 min), 1.5 hr (±5 min), 2.5 hr (±10 min), 4 hr (±15 min), 6 hr (±15 min), 8 hr (±15 min), 10 hr (±30 min) (optional), and 24 hr (±30 min). Refer to the Laboratory Manual for sample handling instructions.

9.5.6 Pharmacogenomic Assessment

Blood draw for pharmacogenomic assessment will be drawn either during Screening or on C1D1 prior to dosing.

9.5.7 Pharmacodynamic Evaluations

For all patients PD evaluations will be performed at screening, pre-dose on Day 1 of each treatment cycle, on Day 15 of Cycle 1, and at the End-of-Study visit for analysis of ctDNA and measurement of circulating plasma levels of, including but not limited to, FGF-2, FGF-23, sVEGFR1, VEGF-A, sCSF-1R, and CSF-1.

Blood samples collected for ctDNA analysis will be processed locally to yield plasma (ctDNA fraction) and buffy coats (genomic DNA fraction). Genomic DNA extracted from the buffy coat or whole blood may be compared to tumor DNA so that molecular alterations unique to the tumor that may modulate response or resistance to study-assigned therapy can be unambiguously identified.

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

Samples may be used for the development of a blood-based diagnostic test.

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

9.5.8 Quality-of-Life Assessments

QoL will be measured using the FACT-B questionnaire (Appendix D), which will be administered on Day 1 of Cycles 1, 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-Study.

9.5.9 Patient Diary

Patient diaries will be provided to patients and should be brought to the site at each visit for review. Patient will use the diary to note the date and dose of lucitanib administration. BP measurements (see Section 9.5.1.3) will also be recorded in the dairy.

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 in the eCRF under specific efficacy assessments. Anticipated fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening are not considered AEs.

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

10.2 Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that occurs at any dose 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 lucitanib should be reported as SAEs
- Is life-threatening (patient is at immediate risk of death from the event as it occurred)
- Requires in-patient hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect

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

- 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 an SAE unless the outcome is fatal during the study or within the safety reporting period. If the event has a fatal outcome during the study or within the safety reporting period, then the event of Progression of Disease must be recorded as an AE and as a SAE with CTCAE Grade 5 (fatal outcome) indicated
- Diagnosis of progression of disease or hospitalization due to signs and symptoms of disease; progression alone should not be reported as SAEs

10.4 Clinical Laboratory Assessments as Adverse Events and Serious Adverse Events

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

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

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

10.5 Pregnancy or Drug Exposure during Pregnancy

If a patient becomes pregnant during the study the investigator is to stop dosing with lucitanib immediately.

A pregnancy is not considered to be an AE or SAE; however, it must be reported to the sponsor using the Pregnancy Report Form within the same timelines as an SAE (Section 10.8). **This applies to female patients as well as female partners of male patients.**

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

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

10.6 Recording of Adverse Events and Serious Adverse Events

AEs will be assessed from the time of first dose of lucitanib through 28 days after the last protocol-specified treatment administration. Study-procedure-related events that occur after signing of the ICF and before administration of lucitanib will also be collected as AEs.

In order to avoid vague, ambiguous, or colloquial expressions, the AE should be recorded in standard medical terminology rather than the patient's own words. Whenever possible, the investigator should combine signs and symptoms that constitute a single disease entity or syndrome. For example, fever, shortness of breath, and cough may be reported as pneumonia, if that is a suspected or final diagnosis.

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

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

SAEs that occur during the study or within 28 days after receiving the last dose of protocol-specified treatment, whether or not related to study drug, must be reported to the sponsor/designee within 24 hours of knowledge of the event (Section 10.8). After the 28-day specified window, only SAEs considered to be treatment-related should be reported.

10.6.1 Intensity of Adverse Events

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

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

10.6.2 Causal Relationship of Adverse Events to Investigational Medicinal Products

Medical judgment should be used to determine the cause of the AE considering all relevant factors such as, but not limited to, the underlying study indication, coexisting disease, concomitant medication, relevant history, pattern of the AE, temporal relationship to the study medication, and 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
- Lucitanib temporarily interrupted
- Lucitanib 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 protocol-specified treatment. Any SAEs must be followed until resolution or stabilization.

10.8 Regulatory Aspects of Serious Adverse Event Reporting

All SAEs, regardless of relationship to study drug, must be reported to the sponsor/designated safety contact within 24 hours of knowledge of the event, according to the procedures below. It is important that the investigator provides an assessment of the relationship of the SAE to study treatment at the time of the initial report. The Clinical Trial Serious Adverse Event Report Form must be used for reporting SAEs.

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

Further details on SAE/pregnancy reporting can be found in the investigator's file.

Clovis or its designee is responsible for submitting reports of AEs associated with the use of the drug that are both serious and unexpected to the U.S. Food and Drug Administration (FDA), according to 21 Code of Federal Regulations (CFR) 312.32 and 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, as applicable. All investigators participating in ongoing clinical studies with the study medication will receive copies of these reports for prompt submission to their IRB or IEC.

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

11 STATISTICAL METHODS

11.1 Analysis Populations

The following analysis populations are defined for the study:

Efficacy Population – all patients who have received at least one dose of lucitanib and are confirmed as *FGFR1*-**,** 11q-amplified, or FGF non-amplified per the central laboratory.

Safety Population – all patients who have received at least one dose of lucitanib.

11.2 Statistical Methods

11.2.1 General Considerations

Patients randomized prior to implementation of Amendment #4 were stratified by FGF aberrancy (*FGFR1*- or 11q-amplified) and prior anti-angiogenic therapy (yes or no) status at baseline. Comparisons of the 15 mg and 10 mg dose groups may be stratified by these same factors. Patients that have amplification of both *FGFR1* and 11q are categorized as FGFR1-amplified for purposes of analysis. Since patients will no longer be randomized to the 15 mg dose group, the comparisons of the *FRGR1*-amplified, 11q-amplified, and FGF non-amplified subgroups will be made for the patients initially treated at 10 mg and for both dose groups.

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. Exact 95% confidence intervals may be presented for frequencies.

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

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

11.2.2 Patient Disposition

The frequency and percentage of patients in each analysis population will be presented. The primary reason for discontinuation of lucitanib will be summarized.

11.2.3 Baseline Characteristics

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

11.2.4 Efficacy Analyses

Kaplan-Meier methodology will be used to summarize the time to event variables. The 25th, 50th (median), and 75th percentiles will be presented along with the Kaplan-Meier estimates of the 6 and 12 month rates. The efficacy results may be presented separately by cohort or the three cohorts together.

11.2.4.1 Progression Free Survival (PFS)

PFS is defined as 1+ the number of days from the date of first dose of study drug to disease progression or death due to any cause, whichever occurs first. Patients without a documented event of progression will be censored on the date of their last adequate tumor assessment (i.e., radiologic assessment), or the date of first dose if no tumor assessments have been performed. Progression events will be determined by the investigator. PFS will be summarized utilizing Kaplan-Meier methodology.

11.2.4.2 Objective Response Rate (ORR)

ORR is the proportion of patients with a best response of CR or PR according to RECIST Version 1.1. The best response is recorded from the start of treatment (Day 1) until disease progression or recurrence. The ORR will be summarized with frequencies and percentages.

11.2.4.3 Duration of Response (DR)

DR for CR and PR will be measured from the date that any of these best responses is first recorded until the first date that PD is objectively documented. DR will be summarized utilizing Kaplan-Meier methodology.

11.2.4.4 Disease Control Rate (DCR)

The DCR is defined as the percentage of patients with a best response rate of CR, PR, or SD for at least 12 weeks. The DCR will be summarized with frequencies and percentages.

11.2.4.5 Overall Survival (OS)

OS is defined as 1+ the number of days from the date of first dose of study drug to death due to any cause. Patients without a documented date of death will be censored on the last date the patient was known to be alive. OS will be summarized utilizing Kaplan-Meier methodology.

11.2.4.6 PK Sub-Study

Comparative PK parameters will include AUC_{0-t}, C_{max}, T_{max}, $T_{1/2}$, V_{SS}/F, and Cl/F for lucitanib and will be determined using noncompartmental methods. AUC_{0-t} will be calculated using the trapezoid rule. The PK parameters will be compared between the tablet and the capsule formulations.

11.2.5 Safety Analyses

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

11.2.5.1 Extent of Exposure

The following will be summarized by individual dose group and by dose group combined:

- Number of cycles initiated
- Number of dose reductions, or interruptions

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

11.2.5.2 Adverse Events

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

The number and percentage of patients who experienced treatment-emergent AEs for each system organ class and preferred term will be presented by individual dose group and by dose groups combined. 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 individual dose group and by dose groups combined.

Separate tables will present the following by cohort:

- All treatment-emergent AEs
- Treatment-emergent AEs by CTCAE Version 4.03 grade
- Grade 3 or greater treatment-emergent AEs
- Treatment-related, treatment-emergent AEs
- Serious treatment-emergent AEs
- Serious treatment-related AEs
- Treatment-emergent AEs with an outcome of death
- Treatment-emergent AEs leading to discontinuation of lucitanib
- Treatment-emergent AEs resulting in interruption, reduction, or delay of lucitanib

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

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

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

11.2.5.3 Clinical Laboratory Evaluations

Clinical laboratory evaluations include the continuous variables for hematology, serum chemistry, and urinalysis. Laboratory values will be presented in 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 lucitanib. The on-treatment period will be defined as the day after the first dose of lucitanib to 28 days after the last dose of lucitanib. 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, median, minimum, and maximum) of the maximum, minimum, and last value during the on-treatment period by dose group. 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. Separate listings will be produced for clinically significant laboratory abnormalities (i.e., those that meet Grade 3 or 4 criteria according to CTCAE Version 4.03) by individual dose group and by dose groups combined.

11.2.5.4 Vital Signs Measurements

The baseline vital signs measurement will be defined as the last value prior to or on the day of the first dose of lucitanib. The on-treatment period will be defined as the day after the first dose of lucitanib to 28 days after the last dose of protocol-specified treatment. Vital signs measurements collected during the on-treatment period will be included in the summary tables. The vital signs measurements collected after the on-treatment period will only be presented in the data listings.

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

11.2.5.5 12-Lead Electrocardiograms

ECG intervals will be stratified into categories indicative of potential clinical significance. Each patient's maximum QT and QT_C intervals from the pre-treatment 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 pre-treatment ECG visit for QT and QT_C, 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.

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

11.2.5.6 Other Safety Measurements

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

11.2.6 Patient Reported Outcomes

PROs will be measured using the FACT-B questionnaire in all patients with both a baseline assessment and at least one post-baseline assessment.

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

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

11.2.7 Population PK Analyses

A separate POPPK data analysis plan will be developed and will outline the detailed approach to data handling, model development and diagnostics, individual model parameter estimation, exploration of covariate effects, and final model evaluation techniques. POPPK analyses and results will be reported separately.

11.2.8 Exploratory Analyses

The exploratory endpoints will be summarized descriptively.

11.3 Sample Size Considerations

Up to 200 patients will be enrolled.

A total of at least 80 patients in the 10 mg arm is sufficient to reliably estimate the median PFS and 6 month PFS rate in these heavily pre-treated patients. An observed median PFS greater than 4 months or a 6-month PFS rate of at least 40% will be sufficient to consider the 10 mg dose group worthy of further study. Therefore, with at least 80 patients treated at 10 mg, the width of the 90% confidence interval for the 6 month PFS rate will be less than ±10%, so that if the observed 6 month rate is 50% then the lower limit on the confidence interval will be greater than 40%.

The treatment effect in Cohort C (biomarker negative sub-group) is not expected to be as large as in Cohorts A and B; however, the same target of 40% will be used to evaluate Cohort C. With 40 patients, the width of the 90% confidence interval for the 6 month PFS rate will be less than ±15%, so that if the observed 6 month rate is less than 25% then the upper limit on the confidence interval will be less than 40%, which is evidence that subsequent studies of 10 mg should exclude biomarker negative patients.

11.4 Interim Analysis

A data monitoring committee (DMC) consisting of two external investigator advisors and specified Clovis personnel will meet approximately quarterly after the first patient is enrolled to review the efficacy and safety data.

A detailed description of the composition, roles and responsibilities, and functioning of the DMC is provided in the DMC Charter.

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, unless in the opinion of the investigator and approved by the sponsor, the patent has indolent progression with evidence of continued clinical benefit from treatment. This must be approved by the sponsor and reviewed on a case by case basis
- Any event, adverse or otherwise, that, in the opinion of the investigator, would pose an unacceptable safety risk to the patient
- An intercurrent illness that, in the opinion of the investigator, would affect assessments of the clinical status to a significant degree and requires discontinuation of therapy
- A positive pregnancy test at any time during the study
- Major non-compliance that may affect patient safety
- Investigator decision

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

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

To the extent possible, end-of-study procedures should be performed on all patients who receive lucitanib. The end-of-study visit should occur 28 ± 7 days following the last dose of lucitanib. After stopping protocol-specified treatment, all patients will remain in the study and will be followed for safety (through 28 days after last dose; those with ongoing SAEs will be followed until either resolution or stabilization has been determined), and for survival status by telephone (at approximately two monthly intervals, until death).

13 STUDY ADMINISTRATION

13.1 Regulatory and Ethical Considerations

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

13.1.1 Regulatory Authority Approvals

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

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

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

13.1.2 Independent Ethics Committee/Institutional Review Board

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

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

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

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

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

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

13.2 Confidentiality of Information

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

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

13.3 Patient Informed Consent

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

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

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

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

13.4 Study Monitoring

On behalf of Clovis, a CRO monitor will contact and visit the investigator at the study center prior to the entry of the first patient and at predetermined appropriate intervals during the study until after the last patient has completed. The 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 in the eCRF and on 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 in the eCRFs.

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

13.5 Case Report Form

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

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

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

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

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

13.6 Study Termination and Site Closure

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

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

The entire study will be stopped if:

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

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the eCRF. All reasons for discontinuation of treatment must be documented.

13.7 Modification of the Study Protocol

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

13.8 Retention of Study Documents

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

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

The investigator shall retain records required to be maintained for a period of 5 years following the date a marketing application in an ICH region is approved for the drug for the indication for which it is being investigated or, if no application is to be filed or if the application is not

approved for such indication, until at least 5 years after the investigation is discontinued. However, these documents should be retained for a longer period if required by the applicable regulatory requirement(s) or if needed by Clovis. In addition, the investigator must make provision for the patients' medical records to be kept for the same period of time.

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

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

13.9 Clinical Study Report

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

13.10 Study Publication

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

13.11 Quality Assurance Audits

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

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15 APPENDICES

Appendix A. Response Evaluation Criteria in Solid Tumors Criteria

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Appendix A
Response Evaluation Criteria in Solid Tumors Criteria

The RECIST guidelines (Version 1.1) are described in Eisenhauer (2009)[56] and at http://www.eortc.be/Recist/Default.htm. A short summary is given below.

Measurability of tumor at baseline

Measurable Disease:

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

1. A minimum size of 10 mm by CT scan (CT scan thickness no greater than 5 mm).
2. A minimum size of 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as non-measurable).
3. A minimum size of 20 mm by chest X-ray.

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

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

Non-measurable Disease:

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

Bone Lesions

Bone lesions, cystic lesion, and lesions previously treated with local therapy require particular comment.

Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic–blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as

measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are non-measurable.

Cystic Lesions

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

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

Lesions with Prior Local Treatment

Tumor lesions situated in a previously 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. Study protocols should detail the conditions under which such lesions would be considered measurable.

Tumor response evaluation

Assessment of overall tumor burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion. In studies where the primary endpoint is tumor progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

Baseline documentation of 'target' and 'non-target' lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of = 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis = 10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Response criteria

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 anti-tumor effect of a treatment.

Evaluation of Target Lesions

Table 6: Evaluation of Target Lesions	
Complete Response	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response	At least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter.
Stable Disease	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum longest diameter since the treatment started.
Progressive Disease	At least a 20% increase in the sum of the longest diameter 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.

Special notes on the assessment of target lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure': While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT scan slice thickness (but should not be changed with varying CT scan slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate,

however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment: When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of Non-target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Table 7: Evaluation of Target Lesions	
Complete Response	Disappearance of all non-target lesions and normalization of tumor marker level.
Stable Disease/Incomplete Response	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.
Progressive Disease	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

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

Special notes on assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows:

When the patient also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. This circumstance arises in some phase 3 trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions

are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increased diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT scan or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

Negative FDG-PET at baseline, with a positive FDG-PET (a 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image) at follow-up is a sign of PD based on a new lesion.

No FDG-PET at baseline and a positive FDG-PET at follow-up:

If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT scan, this is PD.

If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT scan, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT scan that is not progressing on the basis of the anatomic images, this is not PD.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in nonrandomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'.

Time point response

It is assumed that at each protocol specified time point, a response assessment occurs. Table 8 below provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

Table 8: Evaluation of best overall response: patients with measurable and non-measurable disease			
Target Lesions	**Non-target Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not evaluated	No	PR
SD	Non-PD or not evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
NE = Not evaluable.			

When patients have non-measurable disease only (therefore non-target), the following table is to be used.

Table 9: Evaluation of best overall response: patients with non-measurable disease		
Non-target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	On-CR/non-PD[1]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
NE = not evaluable. 1 = 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.		

Missing assessments and inevaluable 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. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

Best overall response: all time points

The best overall response is determined once all the data for the patient is known.

Best response determination in trials where confirmation of CR or PR is not required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Best response determination in trials where confirmation of CR or PR is required: CRs or PRs may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in the following table.

Table 10: Best overall response when confirmation of CR and PR is required

Overall response first time point	Overall response subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD, OR PR[1]
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

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

Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the eCRF.

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PRNE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in the tables above.

Conditions that define 'early progression, early death and inevaluability' are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of CR. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Frequency of tumor re-evaluation

Frequency of tumor re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of phase 2 studies where the beneficial effect of therapy is not known, follow-up every 6–8 weeks (timed to coincide with the end of a cycle) is reasonable. Smaller or greater time intervals than these could be justified in

specific regimens or circumstances. The protocol should specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumor type under study) and how often evaluations are repeated.

Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances certain non-target organs may be evaluated less frequently. For example, bone scans (scintigraphy) may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.

After the end of the treatment, the need for repetitive tumor evaluations depends on whether the trial has as a goal the response rate or the time to an event (progression/death). If 'time to an event' (e.g., time to progression, disease-free survival, PFS) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomized comparative trials in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6–8 weeks on treatment or every 3–4 months after treatment) and should not be affected by delays in therapy, drug holidays, or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.

Confirmatory Measurement/Duration of Response

Confirmation

As ORR is not the primary endpoint, confirmation of response is not required.

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 (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started (if the baseline sum is the smallest, this is the reference for calculation of PD).

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
List of concomitant medications that can prolong the QT interval and increase the risk of causing Torsades de Pointes

Medications linked to prolongation of the QT interval and association with Torsade de Pointes can be accessed at: http://www.crediblemeds.org/everyone/composite-list-all-qtdrugs/?rf=All

Appendix D
FACT-B Version 4.0[57]

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

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some - what	Quite a bit	Very much
GF1	I am able to work (include work at home).....	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun.....	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
B1	I have been short of breath	0	1	2	3	4
B2	I am self-conscious about the way I dress	0	1	2	3	4
B3	One or both of my arms are swollen or tender	0	1	2	3	4
B4	I feel sexually attractive	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
B6	I worry that other members of my family might someday get the same illness I have	0	1	2	3	4
B7	I worry about the effect of stress on my illness	0	1	2	3	4
B8	I am bothered by a change in weight	0	1	2	3	4
B9	I am able to feel like a woman	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4

Appendix E.
Inhibitors and Inducers of CYP2C8 and CYP3A4

CYP Enzyme	Strong Inhibitor (Contraindicated)	Moderate Inhibitor (Use with Caution)
CYP2C8	gemfibrozil	teriflunomide
CYP3A4	boceprevir clarithromycin conivaptan grapefruit juice[1] indinavir itraconazole ketoconazole lopinavir/ritonavir nefazodone nelfinavir posaconazole ritonavir saquinavir telaprevir telithromycin voriconazole	amprenavir aprepitant atazanavir ciprofloxacin darunavir/ritonavir diltiazem erythromycin fluconazole fosamprenavir grapefruit juice[1] imatinib verapamil

CYP Enzymes	Dual Inhibitor (Contraindicated)	Dual Inhibitor (Use with Caution)
CYP3A4 & CYP2C8	clopidogrel verapamil teriflunomide	trimethoprim ticargrelor

CYP Enzyme	Strong Inducer (Contraindicated)
CYP3A4	avasimibe carbamazepine phenytoin rifampin St. John's Wort

[1] The effects of grapefruit juice vary widely among brands, thus can be classified as both a strong and moderate inhibitor depending on concentration, quantity consumed, and preparation. Patients should be advised to avoid.

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#classInhibit