CLINICAL STUDY PROTOCOL

A MULTICENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY OF VARLITINIB PLUS CAPECITABINE VERSUS PLACEBO PLUS CAPECITABINE IN PATIENTS WITH ADVANCED OR METASTATIC BILIARY TRACT CANCER AS SECOND-LINE SYSTEMIC THERAPY

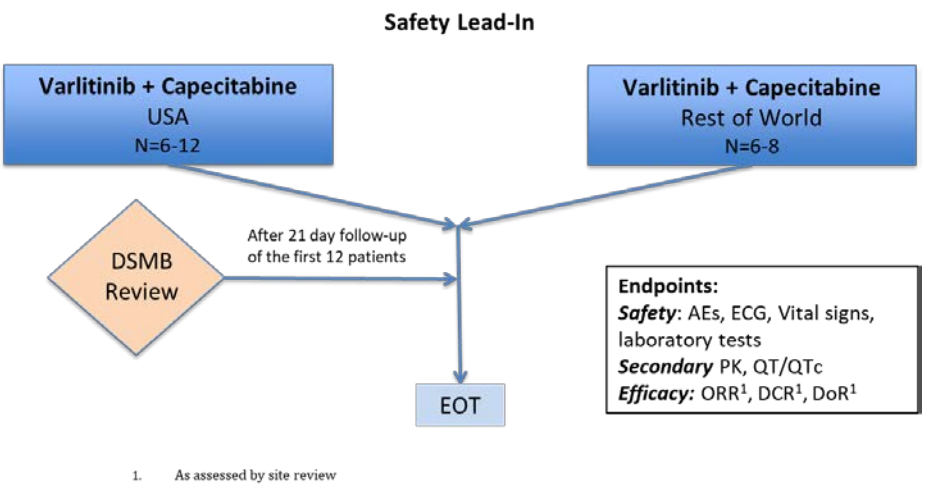
Abbreviated Protocol Title:	Treatment Opportunity with Varlitinib in Biliary Tract Cancer (TreeTopp)
Protocol Number:	ASLAN001-009
EudraCT Number:	2017-000114-30
Investigational Product:	Varlitinib
Phase:	Phase 2/3
Sponsor:	ASLAN Pharmaceuticals Pte. Ltd. 83 Clemenceau Avenue #12-03 UE Square Singapore 239920
Protocol Date:	13 Aug 2019
Protocol Version:	Version 6.0

1 SYNOPSIS

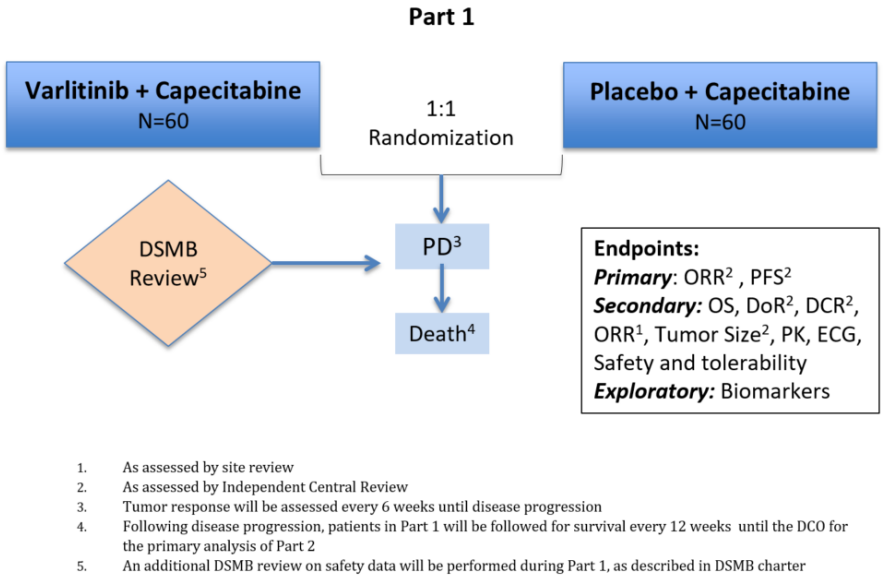
Protocol Number:	ASLAN001-009
Abbreviated Protocol Title:	Treatment Opportunity with Varlitinib in Biliary Tract Cancer (TreeTopp)
Protocol Title	A multicenter, double-blind, randomized, placebo-controlled study of varlitinib plus capecitabine versus placebo plus capecitabine in patients with advanced or metastatic biliary tract cancer as second-line systemic therapy
Investigational Product:	Varlitinib
Study Centers:	Multicenter–United States, Japan, South Korea, Singapore, Taiwan, China, multiple countries in Europe, and the rest of world (ROW)
Phase:	Phase 2/3
Objectives:	**Primary objectives:** Safety lead-in To assess the safety and tolerability of varlitinib 300 mg twice daily (BID) (every day), in combination with capecitabine 1000 mg/m^2 (BID for 14 days followed by a 7-day rest) as measured by the incidence of adverse events (AEs), and changes from baseline in safety parameters. Part 1 To assess the efficacy of varlitinib in combination with capecitabine as measured by co-primary endpoints of objective response rate (ORR) and progression-free survival (PFS), both assessed by an Independent Central Review (ICR). Part 2 To assess the efficacy of varlitinib in combination with capecitabine as measured by overall survival (OS). **Secondary objectives**: Safety lead-in 1. To evaluate the pharmacokinetics (PK) of varlitinib (and any relevant circulating metabolites) and capecitabine (and its active metabolite 5-FU) when given in combination 2. To evaluate the effect of varlitinib on QT/QTc 3. To evaluate the efficacy of varlitinib in combination with capecitabine as measured by ORR, duration of response (DoR) and disease control rate (DCR), all based on site assessment Part 1 1. To evaluate the efficacy of varlitinib in combination with capecitabine, as measured by DoR, and DCR as assessed by ICR, and OS and ORR as assessed by the site 2. To assess the safety and tolerability of varlitinib when combined with capecitabine 3. To explore exposure-response relationships for varlitinib (and any relevant circulating metabolites) for measures of efficacy, safety, and pharmacological responses

	4. To examine the effects of varlitinib, when added to capecitabine on ECG parameters including QTcF, QTcB, HR (heart or ventricular rate), PR and QRS Part 2 1. To evaluate the efficacy of varlitinib in combination with capecitabine, as measured by ORR, DoR, DCR and PFS, all based on site assessment 2. To assess the safety and tolerability of varlitinib when combined with capecitabine 3. To explore exposure-response relationships for varlitinib (and any relevant circulating metabolites) for measures of efficacy, safety, and pharmacological responses via sparse PK sampling and population PK analyses **Exploratory objectives:** Part 1 1. To explore the role of human epidermal growth factor family of receptors (HER) status as a predictor of benefit to varlitinib 2. To explore possible relationships between HER family and downstream signaling protein and phospho-protein expression levels and clinical outcomes 3. To explore possible relationships between gene mutational status and clinical outcomes Part 2 If a relationship is found between biomarker(s) expression and clinical outcomes in Part 1 of the study, the biomarker(s) could be prospectively evaluated in Part 2 of the study.

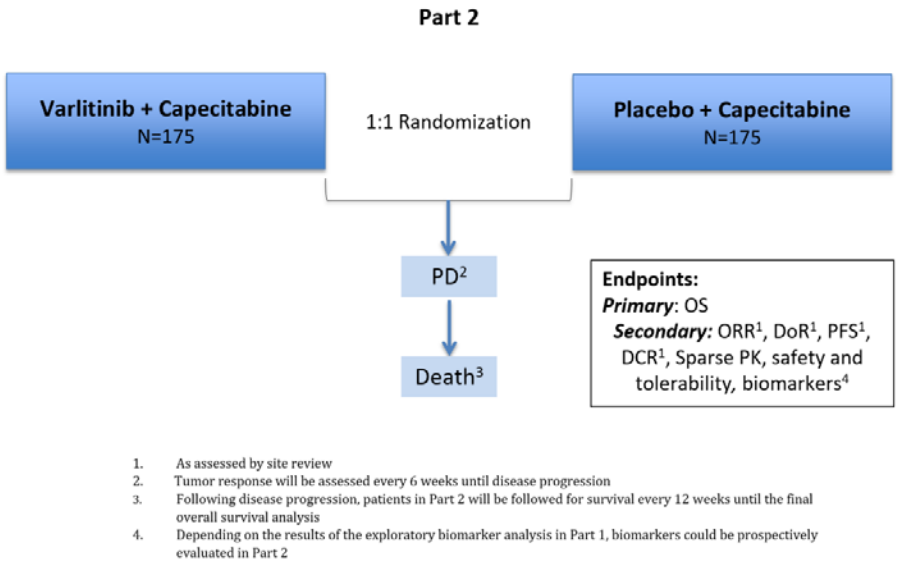
Study Design:



This study will commence initially with a Safety lead-in group. This part of the study is a single arm, open label design to assess the safety of varlitinib (300 mg BID, every day) plus capecitabine (1000 mg/m^2 administered BID every day for 14 days, followed by a 7 day rest period) in a small set of patients (12 to 20 patients) with 12 patients completing the PK and ECG evaluation. Treatment will continue until disease progression or development of unacceptable toxicity or consent withdrawal or death.



Part 1 of the study is designed as a double-blind, randomized, placebo controlled study to assess the efficacy and safety of varlitinib (300 mg BID) plus capecitabine (1000 mg/m^2 BID for 14 days out of 21 days) in comparison with placebo plus capecitabine in approximately 120 patients. Eligible patients will be randomized to varlitinib or placebo in a 1:1 ratio. Treatment will continue until disease progression or development of unacceptable toxicity or consent withdrawal or death.



Part 2 of the study is designed as double-blind, randomized, placebo controlled study to confirm the efficacy of varlitinib plus capecitabine compared to capecitabine in approximately 350 patients. Part 2 will follow the same design and treatment schedule as Part 1. This part of the study will commence following review of the Part 1 results.

Number of Patients:

<u>Safety lead-in</u>

A total of 12 to 20 eligible patients will be enrolled to receive varlitinib plus capecitabine.

United States: 6 to 12 eligible patients are expected to be enrolled from the United States.

Rest of the World: An additional 6 to 8 eligible patients will be enrolled from the rest of the world.

Patients in this group will be replaced if varlitinib compliance is <85% in the first 14 days. Pharmacokinetic sampling will be performed in approximately 12 patients.

<u>Part 1</u>

Approximately 120 eligible patients will be enrolled and randomized in a 1:1 ratio to receive varlitinib and capecitabine (n=60) or placebo and capecitabine (n=60).

<u>Part 2</u>

Approximately 350 eligible patients will be enrolled and randomized in a 1:1 ratio to receive varlitinib and capecitabine (n=175) or placebo and capecitabine (n=175)

In both Part 1 and Part 2 of the study, patients will be stratified by:

- region - US and the ROW and;
- primary tumor location - gallbladder vs non-gallbladder

Treatment:	Safety lead-in Per oral (PO) varlitinib 300 mg BID, every day. PO capecitabine 1000 mg/m^2 BID from Day 1 to Day 14 followed by 7-day of rest period, every 21 days. Treatment will continue for a minimum of 14 days, during which dose adjustment is not allowed. Dose adjustment and interruption is allowed from day 15 onwards. Treatment will continue in 21-day cycles until disease progression, development of unacceptable toxicity, withdrawal of consent, or death. Part 1 and Part 2 PO varlitinib 300 mg (if assessed as safe in Safety lead-in) or matching placebo, both BID, every day PO capecitabine 1000 mg/m^2 BID from Day 1 to Day 14 followed by a 7-day of rest period, every 21 days Treatment will continue until unacceptable toxicity, disease progression, withdrawal of consent or death. Dose modification will be permitted where required according to protocol.
Study Duration:	**Screening Period:** Up to 14 days. It may be extended up to 21 days subjected to a case by case review and approval by the Sponsor. **Treatment Period:** Safety lead-in Study treatment will be given in 21-day cycles. Patients will receive study medication until disease progression, unacceptable toxicity, withdrawal of consent or death. Patients will be followed for disease status every 6 weeks. Part 1 and Part 2 Study treatment will be given in 21-day cycles. Patients will receive study medication until disease progression, development of unacceptable toxicity, withdrawal of consent or death. Patients will be followed for disease status every 6 weeks during treatment period and follow-up period until disease progression. Patients who discontinue treatment for reasons other than disease progression will be followed for disease status every 6 weeks until disease progression. **Follow-up Period:** Patients will complete a safety follow-up visit 28 days after the last dose of varlitinib therapy. All patients will be followed for survival and status of further anti-cancer treatment every 12 weeks until death or until the data cut-off (DCO) for the final overall survival analysis. **Part 1** After the DCO for the primary analysis of ORR and PFS, patients who are ongoing on the trial will continue to be followed for survival every 12 weeks. The OS follow-up analysis is planned when approximately 95 OS events have occurred. Note, survival calls may be made in the week following the date of Data Cut Off (DCO) for the analyses, and if subjects are confirmed to be alive or if the death date is after the DCO, these subjects will be censored at the date of DCO.

Study Population:	**Inclusion Criteria:** Patients will be eligible for the study if they: 1. Are of or older than the legal age in the respective countries at the time when written informed consent is obtained 2. Have histologically or cytologically confirmed advanced (unresectable) or metastatic biliary tract cancer, including intrahepatic or extrahepatic cholangiocarcinoma (CCA), gallbladder cancer and carcinoma of Ampulla of Vater. This includes clinical diagnosis of biliary tract cancer with histological confirmation of adenocarcinoma. 3. Have received and failed one and only one prior line of systemic treatment for advanced or metastatic disease with radiologic evidence of disease progression. This prior line of systemic treatment must also contain gemcitabine 4. Have received at least 6 doses of gemcitabine containing treatment in first line (Adjuvant therapy is not regarded as 1st line therapy) 5. Have radiographically measurable disease based on Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 as assessed by Independent Central Review (ICR) (For Part 1) 6. Have no evidence of biliary duct obstruction, unless obstruction is controlled by local treatment or, in whom the biliary tree can be decompressed by endoscopic or percutaneous stenting with subsequent reduction in bilirubin to below or equal to 1.5 × upper level of normal (ULN) 7. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 8. Are able to understand and willing to sign the informed consent form 9. Have adequate organ and hematological function: a. Hematological function, as follows: • Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L • Platelet count $\geq 100 \times 10^9$/L b. Renal functions, as follows: • Estimated glomerular filtration rate or creatinine clearance > 50 mL/min/1.73m2 c. Hepatic function, as follows: • Albumin ≥ 3 g/dL • Total bilirubin ≤ 1.5 × ULN • Aspartate aminotransferase and alanine aminotransferase ≤ 5 × ULN **Exclusion Criteria:** Patients will be ineligible for the study if they: 1. Are currently on or have received anti-cancer therapy within the past 3 weeks before receiving the first dose of study medication 2. Are currently on or have received radiation or local treatment within the past 3 weeks for the target lesion(s) before receiving the first dose of study medication 3. Have evidence of multiple (≥ 2) peritoneal metastases or ascites at baseline as assessed by ICR (For Part 1). (Ascites which can be attributed by non-malignant causes is not excluded. Minimal ascites, which does not require paracentesis is permitted.) 4. Have had major surgical procedures within 14 days prior to first dose of study medication 5. Have a known metastatic brain lesion(s), including asymptomatic and well controlled lesion(s) 6. Have malabsorption syndrome, diseases significantly affecting gastrointestinal function, resection of the stomach or small bowel, or difficulty in swallowing

	and retaining oral medications which in the opinion of the Investigator could jeopardize the validity of the study results 7. Have uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, unstable angina pectoris, cardiac arrhythmia, diabetes, hypertension, or psychiatric illness/social situations that would limit compliance with study requirements 8. Have any history of other malignancy unless in remission for more than 1 year (non-melanoma skin carcinoma and carcinoma-in-site of uterine cervix treated with curative intent is not exclusionary) 9. Are female patients who are pregnant or breast feeding 10. Have been previously treated with varlitinib or have been previously treated with capecitabine as first line therapy for advanced or metastatic disease. For patients who have previously received capecitabine as a radiosensitizer or as part of their adjuvant therapy and their disease has relapsed for more than 6 months after their last dose of capecitabine adjuvant therapy, their capecitabine therapy will not be considered as a line of systemic chemotherapy for metastatic/advanced disease, and thus they can participate in the study 11. Have received any investigational drug (or have used an investigational device) within the last 14 days before receiving the first dose of study medication 12. Have unresolved or unstable serious toxicity (≥ common terminology criteria for adverse events [CTCAE] 4.03 Grade 2), with the exception of anemia, asthenia, and alopecia, from prior administration of another investigational drug and/or prior cancer treatment 13. Have a known positive test for human immunodeficiency virus, hepatitis C (treatment naïve or after treatment without sustained virologic response), or hepatitis B infection with hepatitis B virus deoxyribonucleic acid exceeding 2000 IU/mL 14. Have a known history of drug addiction within last 1 year which, in the opinion of the Investigator, could increase the risk of non-compliance to investigational product 15. Need continuous treatment with proton pump inhibitors during the study period 16. Have a history of (non-infectious) pneumonitis that required steroids or current pneumonitis, or have a history of interstitial lung disease or current interstitial lung disease 17. Have any history or presence of clinically significant cardiovascular, respiratory, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic or psychiatric disease or any other condition which in the opinion of the Investigator could jeopardize the safety of the patient or the validity of the study results 18. Have a baseline corrected QT interval (Fridericia's formula) (QTcF) > 450 ms or patients with known long QT syndrome; torsade de pointes; symptomatic ventricular tachycardia; an unstable cardiac syndrome in the past 3 months before screening visit; > class 2 New York Heart Association heart failure; or > class 2 angina pectoris; or receiving quinidine, procainamide, disopyramide, amiodarone, dronedarone, arsenic, dofetilide, sotalol, or methadone. Please also see prohibited medication/therapy (Section 5.4.10.1)
Study Endpoints:	**Primary Endpoints:** Safety lead-in • Incidence of AEs, categorized in accordance to CTCAE 4.03 and changes from baseline in safety parameters (including vital signs, ECG parameters, clinical laboratory tests) Part 1

- ORR: Defined as the proportion of patients with a best objective response of complete response (CR) or partial response (PR), as assessed by ICR defined by the RECIST v1.1 criteria.
- PFS: Defined as the time from randomization until the date of objective disease progression or death (by any cause in the absence of disease progression). Progression is defined in accordance with the RECIST v1.1 criteria will derived programmatically based on data from the ICR of radiological data.

Part 2

- OS: Defined as the time from randomization until death by any cause. Any patient not known to have died at the time of DCO will be censored based on the last recorded date on which the patient was known to be alive.

Secondary Endpoints:

Safety lead-in

- Pharmacokinetics endpoints: The PK of varlitinib (and any relevant circulating metabolites) and capecitabine and 5-FU (active metabolite of capecitabine) will be determined at selected time points (pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8.5, 10, and 12 hours post-dose). Other relevant circulating metabolites of capecitabine (5'-DFCR, 5'-DFUR, and FBAL) will only be determined if this is considered necessary based on the pharmacokinetic and safety findings). The following PK parameters will be evaluated where possible:
  Cycle 1 Day 1, Day 8 and Day 14:
  - maximum plasma concentration (C_{max})
  - time to C_{max}(t_{max})
  - plasma concentration before next dose (C_{trough})
  - area under the plasma concentration-time curve from 0 to 12 hours ($AUC_{0-\tau}$)
  - half-life ($t_{1/2}$)
  - apparent clearance (Cl/F)
  - apparent volume of distribution (V_z/F)
  - apparent volume of distribution at the steady state (V_{ss}/F)
  - where τ = 12 hours (dosing interval)

  Cycle 1 Day 8
  - accumulation ratio of $AUC_{0-\tau}$ ($RacAUC_{0-\tau}$) (Day 8/Day 1)
  - accumulation ratio of C_{max} $RacC_{max}$ (Day 8/Day 1)

  Cycle 1 Day 14
  - accumulation ratio of $AUC_{0-\tau}$ ($RacAUC_{0-\tau}$) (Day 14/Day 1)
  - accumulation ratio of C_{max} $RacC_{max}$ (Day 14/Day 1)
- Exploratory electrocardiogram endpoints: QTcF, QTcB, PR, QRS, HR
- Efficacy endpoints
  - ORR: as determined by site review of radiological data.
  - DoR: Defined as the time, in days, from the first recorded achievement of a response (PR or above) until time of objective disease progression in the subset of patients classified as responders in the assessment of ORR
  - DCR: Defined as the proportion of patients with a best response of stable disease maintained for at least 12 weeks (-5 days) from randomization, PR or CR as defined by RECIST v1.1 criteria.

Part 1

- Efficacy Endpoints
  - OS

	- DoR - DCR - ORR as based on site review of radiological data - Tumor size: Defined as the percentage change from baseline in the sum of target lesions at Week 12 ($(\%\Delta TS_{Wk12})$ • Safety Endpoints - Incidence of AEs, categorized in accordance to CTCAE 4.03 and changes from baseline in safety parameters (including vital signs, ECG parameters, clinical laboratory tests) • Electrocardiogram Endpoints - QTcF, QTcB, PR, QRS, HR • PK Endpoints PK samples will be obtained for the PK evaluation of varlitinib (and any relevant circulating metabolites). PK samples will be collected at the following time points for all patients: - Cycle 1 Day 1: 5 minutes pre-dose, 1.5 hours, 3 hours, 5 hours, and 8 hours post-dose - Cycle 1 Day 8: 20 minutes pre-dose, 1.5 hours, 3 hours, 5 hours, and 8 hours post-dose - End of study after full drug washout: 28 days after last dose at the patient's safety follow-up visit <u>Part 2</u> • Efficacy Endpoints (all based on site review of radiological data) - ORR - DoR - DCR - PFS • Safety Endpoints - Incidence of AEs, categorized in accordance to CTCAE 4.03 and changes from baseline in safety parameters (including vital signs, clinical laboratory tests) • PK Endpoints - A population PK study with sparse sampling will be included in the Part 2 of the study to explore exposure-response relationships for varlitinib (and any relevant circulating metabolites) for measures of efficacy, safety, and pharmacological responses via sparse PK sampling and population PK analyses. **Exploratory Endpoints:** <u>Part 1 only</u> Possible relationships between protein and phospho-protein expression levels and clinical outcome, and gene mutational status and clinical outcome will be explored using proteins and genes including, but not limited to: • Via IHC: - epidermal growth factor receptor (EGFR), pEGFR - HER2, pHER2 - HER3, pHER3 - HER4, pHER4 • Via PCR/Sequencing - Mutational status of genes, such as *KRAS, NRAS, BRAF*, *EGFR, HER2* and other genetic factors that may affect response to therapy.

	The protein and gene studies will be conducted using archival material (and if not available, biopsy tissue samples). If a relationship is found between biomarker(s) expression and clinical outcomes in Part 1 of the study, the biomarker(s) could be prospectively evaluated in Part 2 of the study.
Study Assessments:	**Safety Evaluations:** Patient safety will be evaluated based on the incidence of AEs and serious AEs (SAEs), physical examination, vital signs (blood pressure [systolic and diastolic], heart rate, respiratory rate, weight, and body temperature), electrocardiogram (ECG) parameters (Safety lead-in and Part 1), and clinical laboratory tests (hematology, clinical chemistry, coagulation and urinalysis). All AEs will be evaluated according to NCI-CTCAE 4.03 and will be captured from the time of informed consent and continue until the safety follow-up assessment (28 days after last administration of study treatment). For the purpose of this study, fluctuations of pre-existing conditions that do not represent a clinically significant exacerbation or worsening need not be considered AEs. In addition, progression of the cancer of target disease under study is generally not considered an AE. <u>Safety lead-in:</u> In the Safety lead-in, triplicate 12-lead ECG will be performed on Cycle 1 Day 1 and Cycle 1 Day 8 at the following time points and will be analyzed by a Core ECG Laboratory: • Cycle 1 Day 1: 45 minutes pre-dose, 5 minutes pre-dose, 1, 2, 3, 4, 5, 6, 8.5, and 12 hours post-dose • Cycle 1 Day 8: 45 minutes pre-dose, 5 minutes pre-dose, 1, 2, 3, 4, 5, 6, 8.5, and 12 hours post-dose Triplicate ECGs will also be collected 3 hours post-dose Day 22 (Cycle 2 Day 1) and onwards every cycle while the subject remains in the study. The 12-lead ECGs will be taken in the supine position, after the patient has been lying down for at least 10 minutes in a quiet environment. Detailed instructions will be described in the ECG manual. The ECG machines supplied by the Core ECG Laboratory will be used for all ECG collection, and the digital files of each tracing will be archived. <u>Part 1:</u> The primary electrocardiographic analysis of the protocol will be from the time-based ECG analysis performed in Part 1 at baseline, Cycle 1 Day 1, Cycle 1 Day 8, and the safety follow-up visit. Triplicate ECGs will be collected with a PK sample collected immediately following ECG acquisition. ECGs will be analyzed by a Core ECG Laboratory. Collection time points: • Cycle 1 Day 1: 45 minutes pre-dose, 5 minutes pre-dose, 1.5, 3, 5 and 8 hours post-dose. Concomitant PK samples will be collected immediately after the ECG collections, except for the 45 minutes pre-dose time points where no PK sample will be collected. • Cycle 1 Day 8: 45 minutes pre-dose, 5 minutes pre-dose, 1.5, 3, 5, and 8 hours post-dose. Concomitant PK samples will be collected immediately after the ECG collections, except for the 45 minutes and 5 minutes pre-dose time points. One pre-dose PK sample will be collected at the 20 minutes pre-dose time point. • End of Study after full drug washout (28 days after the last dose) a set of triplicate ECGs will be collected 3 hours after a light snack.

	In addition, triplicate safety ECGs will be collected 3 hours post-dose on Day 22 (Cycle 2 Day 1), Day 64 (Cycle 4 Day 1) and every 2 cycles while the subject remains in the study. This data will not be analyzed by the Core ECG Laboratory but will be assessed by the investigator. The digital ECGs will be archived. Part 2: ECGs will be collected in Part 2 of the study as part of standard safety monitoring at screening, baseline (before a snack), and 3 hours post-dose on Day 22 (Cycle 2 Day 1), Day 64 (Cycle 4 Day 1) and every 2 cycles while the subject remains in the study. These data will not be analyzed by the Core ECG Laboratory but assessed by investigators. A data safety monitoring board (DSMB) will meet on 2 specified occasions to review safety data; the first DSMB will occur after the first 12 patients in the Safety lead-in have completed the 21 days of follow-up and the second DSMB will be at a selected time point to be confirmed during Part 1 of the study. Additional DSMB meetings may occur if needed. Details will be specified in the DSMB Charter. **Efficacy Evaluations:** Tumor evaluations will be performed to evaluate the efficacy of treatment according to RECIST v1.1. Tumor response will be assessed by means of computed tomography (CT) or magnetic resonance imaging (MRI) at baseline and every 6 weeks until EOT (Safety Lead-in) or disease progression (Part 1 and Part 2). All tumor responses should be assessed at every assessment time point using the same methods (contrast-enhanced CT or MRI) used to characterize lesions identified at baseline. Safety Lead-in Radiological images collected in the Safety lead-in will be assessed by the site. Part 1 Radiological images collected in the Part 1 of the study will be assessed by an ICR. Patients cannot be randomized into Part 1 of the study until the ICR has confirmed eligibility. Central radiological reading will not interfere with the Investigator's judgment on disease progression. The co-primary endpoints of ORR and PFS will be programmatically derived using the ICR's assessment of the radiological data in Part 1. Objective response rate as determined by the site review will also be reported as a secondary endpoint. Part 2 All efficacy endpoints based on radiological data in Part 2 will be programmatically derived based on data provided by the site review of the Part 2 radiological data. Part 1 and 2 only Blood to be collected for analysis of cancer antigen 19.9 (CA19.9) and carcinoembryonic antigen (CEA) every 6 weeks starting from Week 6. Archival paraffin-embedded tumor tissues will be collected during screening for future analysis if the patient has provided the optional tumor tissue consent.

	Biopsies will be performed during screening for those patients who did not have enough archival tumor tissue if the patient has provided the optional tumor tissue consent. **Pharmacokinetic Evaluations:** Safety Lead-in Blood samples for PK analysis of varlitinib (and any relevant circulating metabolites), capecitabine, and 5-FU (metabolite of capecitabine) will be collected at the following time points in the Safety lead-in part only: • Cycle 1 Day 1: 5 minutes pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8.5, 10, and 12 hours post-dose • Cycle 1 Day 8: 20 minutes pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8.5, 10, and 12 hours post-dose • Cycle 1 Day 14: 5 minutes pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8.5, 10, and 12 hours post-dose When ECGs and PK samples are collected at the same time point, the PK samples are always collected after the ECGs. In addition, unscheduled PK samples collected 7 days following dose reduction of varlitinib at any cycle of treatment will include: up to 5 minutes pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8.5, 10, and 12 hours post-dose, if required. Part 1 and Part 2 PK samples will be obtained for the PK evaluation of varlitinib (and any relevant circulating metabolites). PK samples will be collected at the following time points: Part 1 (All patients) • Cycle 1 Day 1: 5 minutes pre-dose, 1.5, 3, 5, and 8 hours post-dose • Cycle 1 Day 8: 20 minutes pre-dose, 1.5, 3, 5, and 8 hours post-dose • End of study after full drug washout: 28 days after last dose at the patient's safety follow-up visit When ECGs and PK samples are collected at the same time point, the PK samples are always collected after the ECGs. Part 2 (Sparse Sampling) • Cycle 1 Day 1: 5 minutes pre-dose, 1-3 hours post-dose, 3-5 hours post-dose, and 5-8 hours post-dose • Cycle 2 Day 1: 20 minutes pre-dose, 1-3 hours post-dose, 3-5 hours post dose, and 5-8 hours post-dose In order to maintain the double-blind design of the study, blood samples will be collected from patients in both groups for plasma measurements of varlitinib and its potential relevant metabolites. In addition, unscheduled PK samples will be collected at least 7 days following dose reduction of varlitinib at any cycle of treatment: up to 5 minutes pre-dose and 3-5 hours post-dose. **Biomarker Evaluations:** Blood samples for potential retrospective analysis of potential biomarkers will be collected at baseline and post Week 6 treatment tumor assessment.
Prohibited	Please see Appendix 14.3 for a complete list

Medications	Any other antitumor treatment, proton pump inhibitors, warfarin, strong CYP3A4 inhibitors, investigational products, and herbal preparations are prohibited throughout this study. H2 blocker can be given 3 hours after each dose of varlitinib. Safety lead-in and Part 1 (2 weeks prior to first dose up to and including Cycle 2 Day 1) Use with caution: Non-excluded drugs that are associated with torsade de pointes and QTc prolongation (Appendix 14.4) or QT prolongation without torsade de pointes (Appendix 14.5) should be at steady-state dosing for at least 2 weeks before enrollment. The dose of such drugs should not be increased, and new drugs in either group should not be initiated without the medical monitor's approval. Safety lead-in and Part 1 (from Cycle 2 Day 2 onwards) Use with caution: Non-excluded drugs that are associated with torsade de pointes and QTc prolongation (Appendix 14.4) or QT prolongation without torsade de pointes (Appendix 14.5) should be at steady-state dosing for at least 2 weeks before enrollment. From Cycle 2 Day 2 onwards, the dose of drugs associated with torsade de pointes and QTc prolongation (Appendix 14.4) or QT prolongation without torsade de pointes (Appendix 14.5) ideally should not be increased. Every attempt should be made to minimize the initiation of such drugs (Appendix 14.4 or Appendix 14.5). The initiation of any such drugs (Appendix 14.4 or Appendix 14.5) requires the medical monitor's approval. Varlitinib may cause a drug-drug interaction with other medications that are cytochrome P450 (CYP) 3A4, CYP2C8, or CYP2C9 inducers, inhibitors, or substrates. CYP3A4 is the major metabolic enzyme of varlitinib, and CYP2C8 only a minor enzyme. Due to the potential for drug interactions based on in vitro screens, concomitant use of moderate CYP3A4, CYP2C8, CYP2C9, and P-gp inducers or inhibitors will be recorded during the entire clinical study.
Statistical Analysis:	Safety lead-in All safety data will be listed and summarized using appropriate descriptive statistics. Full details will be provided in the statistical analysis plan (SAP). The pharmacokinetic endpoints of varlitinib, capecitabine and 5-FU will be plotted and summarized using descriptive statistics. QTcF exposure response modeling, along with time-based central tendency effects and categorical QTc analyses will be evaluated. Both the Bazett and Fridericia correction (primary correction method) formulae will be used to estimate QTc. Parts 1 and 2 For Part 1 and 2, all primary and key secondary efficacy endpoints will be analyzed based on the *Full Analysis Set* (FAS) using an intention-to-treat principle. Patients who were randomized but did not subsequently go on to receive study treatment will be included in the FAS. Analyses performed in the protocol-defined "Evaluable for Response set (EFR)" will be supportive. Objective response rate will be analyzed using a stratified exact binomial test (Mehta et al, Emerson) which extends Fisher's Exact test to more than one stratum. The analysis will be stratified by primary tumor location (GB/non-GB). The 2-sided p-value will be obtained by doubling the 1-sided p-values.

	To test for heterogeneity across strata, the exact test of Zelen will be performed testing whether the treatment effect differs between the 2 strata included in the primary analysis. Progression-free survival will be analyzed using a stratified log-rank test using the Breslow method to handle ties (Breslow, 1974). The analysis will be stratified by primary tumor location (GB/Non-GB). Overall survival will be analyzed using the methods outlined above for PFS. For Part 1, OS will be analyzed twice. A preliminary analysis of OS will be performed at the time of the primary analysis of ORR and PFS. It is anticipated that the OS data at this time will be immature, thus a second analysis of OS is planned for when approximately 95 patients (approx. 79%) have an OS event. The second analysis of OS will be considered the primary analysis of OS for Part 1 of the trial. For Part 2, the primary analysis of OS will be performed when 247 patients have experienced an OS event. Further details will be provided in the study SAP. Duration of response will be listed and summarized descriptively for the duration of response in responding patients, including the associated Kaplan-Meier curves. Disease control rate will be analyzed using the methods described above for ORR. Tumor size is a secondary endpoint in Part 1 and will be used to assess the exploratory objective of evaluating the role of HER family expression levels as predictors of benefit to varlitinib. Tumor size will be analyzed by analysis of covariance (ANCOVA). Plasma sampling will be conducted for population PK evaluation in Parts 1 and 2 of the study and will use an NLME. PK sampling of all patients is planned for Part 1 of the study while sparse PK sampling is planned for Part 2. For the sparse PK sampling in Part 2, the double-blind design will be maintained and blood samples will be collected from a selected number of patients without limiting the sampling to varlitinib patients only. All PK data will be analyzed according to treatment received. Deviations that have the potential to significantly affect the PK will be reviewed. The population, and decisions regarding which profiles are usable, will be defined by the Study Team Physician, Pharmacokineticist, and Statistician prior to unblinding or any analyses being performed. <u>ECG/QT Analysis (Safety Lead-in and Part 1)</u> *General Principles* Baseline will be defined as the mean of the triplicate ECG readings performed pre-dose on Day 1. On Day 1, pre-dose is defined as 2 sets of triplicate ECGs taken 45 minutes and 5 minutes prior to dosing. The ECG values from these 2 sets of ECGs will be averaged to create the baseline value. Similarly, for all other time points, for each ECG parameter, each patient's mean will be calculated from the triplicate readings and the mean value will be used. The final ECG assessments (including interval measurements) will be made by the Core ECG laboratory. The Part 1 electrocardiographic Core ECG Laboratory assessments constitute the study's primary assessment of ECG/QTc. Any analysis of ECG data from the Safety lead-in is considered exploratory. Due to the non-randomized, open label design of the Safety lead-in, data from the Safety lead-in will be presented separately from data from Part 1 of the study. Furthermore, ECG/QT outputs will be made available to the DSMB for consideration when determining whether the study should progress to Part 1.

	Methods of Analysis For the Safety lead-in, exploratory descriptive and categorical analyzes, including change from baseline will be performed to investigate the impact of varlitinib and capecitabine treatments on the changes from baseline in ECG parameters. The ECG parameters of interest include: QT including QTcF and QTcB, HR, PR, QRS intervals. For Part 1, a multi-step approach will be applied to evaluate the effect of capecitabine alone and varlitinib in combination with capecitabine on the ECG parameters at different time points post-dose. The comparisons will be done between ECG values at each time point post-dose and baseline and between treatment arms with and without varlitinib for each time point individually. The evaluation of the cardiodynamic effects of capecitabine and varlitinib may be explored using exposure-response modeling if there appears to be a meaningful effect of varlitinib when added to capecitabine on the ECG parameters including QTcF. This will be further described in the SAP. Central Tendency Analysis For both the Safety lead-in and Part 1, the change from baseline in QTcF, PR, QRS, QTcB, and heart rate, will be summarized by time point (and treatment arm for Part 1) using descriptive statistics (n, mean, SD, min, median, max, 90% confidence intervals). Categorical Analyses For both the Safety lead-in and Part 1, the following will be summarized: • The proportion of patients obtaining treatment-emergent absolute QTcF values > 450 msec and ⩽ 480 msec; > 480 msec and ≤ 500 msec; and > 500 msec • The proportion of patients obtaining a QTcF increase from baseline values ⩾ 30 and <60 msec and ⩾ 60 msec • The proportion of patients obtaining a QRS change from baseline > 25% resulting in QRS > 120 msec • The proportion of patients obtaining a PR interval change from baseline >25% reaching a value >220 msec • The proportion of patients obtaining a > 25% decrease from baseline in heart rate resulting in a heart rate < 50 beats per minute (bpm) or a > 25% increase from baseline in heart rate resulting in a heart rate > 100 bpm For Part 1, the above categorical data summaries will be presented by treatment arm. Morphological T-wave Analysis T-wave morphology will also be analyzed, focusing on change from baseline, i.e., treatment emergent changes. Following Part 1, a formal statistical analysis will be performed to assess the potential impact of varlitinib and capecitabine on changes in ECG parameters.

	The statistical stepwise approach will be used to separate the cardiodynamic effect of varlitinib from normal circadian fluctuation in the ECG values and from the effect of capecitabine: 1. ANOVA mixed effects comparison of the absolute values of ECG parameters at each time point vs baseline using treatment as a fixed effect in order to evaluate the contribution of circadian fluctuation and to determine how treatment differences contribute to the changes. The ECG parameter values will be log-transformed and the resulting output will include the geometric mean ratio for test vs reference with the corresponding confidence interval and p-value. Interaction term, time point x treatment, will be also evaluated if the data allow. 2. ANOVA comparison of the absolute values of ECG parameters as well as change from baseline (ΔECG) between treatments for each post-dose time point assessed separately in order to separate the varlitinib effect from that of capecitabine. The ECG parameter values will be log-transformed and the resulting output will include the geometric mean ratio for test vs reference with the corresponding confidence interval and p-value. ΔECG will be tested as untransformed and log-transformed parameters to avoid bias from discarding 0 ΔECG values from the comparisons. 3. Exposure-Response Analysis: Linear mixed effect model between ΔQTcF and time matched concentrations of varlitinib and other potential metabolites if measured and as appropriate. Other ECG variable may be similarly analyzed and other models used, if appropriate. 3.1. ΔQTcF will be calculated as the difference between each time point value and the average baseline value for each arm with the combination varlitinib/capecitabine treatment. 3.2. ΔΔQTcF will be calculated for each patient in the combination arm individually as the difference between the ΔQTcF value for the arm with combination varlitinib/capecitabine treatment and the average value of all patients in the capecitabine alone arm matching time point. Other ECG parameters may also be used in the analysis including QTcB, heart rate, etc to provide supporting information. 3.3. Base linear mixed effect model will include patients as a random effect. 3.4. The total dose of capecitabine may be included as a fixed effect in the model to account for differences in total doses received by subjects with different body surface area. 4. Linear mixed effect model between ΔQTcF parameters and time matched concentrations of capecitabine and 5-FU (metabolite of capecitabine) and other potential metabolites if measured and as appropriate 4.1. ΔQTcF will be calculated for all patients in both arms as the difference between each time point value and the average baseline value. 4.2. Base linear mixed effect model will include patients as a random effect and treatment (capecitabine alone or in combination with varlitinib) as a fixed effect; the total capecitabine dose may also be used as a fixed effect. 5. Different covariates may be included in the complex models in addition to the base model as fixed effects such as time point in order to ensure the model feasibility and to evaluate covariates influential to ECG parameters. The results of the fitted models will be presented using statistical parameters such as the geometric mean ratios and corresponding confidence intervals (for ANOVA) and estimates of the slope, and associated confidence interval for the linear mixed effect models. In addition, graphic exploration of the exposure-ECG relationship may be performed:

	• Residual plots to predict results • Double Y plots with time on the X axis and time matched values of PK concentrations for varlitinib and capecitabine on the Y1 axis, ΔECG on the Y2 axis to determine the possibility of hysteresis between drug concentration and cardiodynamic effects • Regression/scatter plots with time matched concentrations of varlitinib and capecitabine on the X axis and ΔECG on the Y axis • Regression/scatter plots with varlitinib or capecitabine non-compartmental PK parameters of C_{max}, C_{trough}, AUC_{tau} and others on the X axis and maximum ΔECG on the Y axis • Forest plots for different categories in ECG changes vs mean (SD) non-compartmental PK parameters for varlitinib or capecitabine on the X axis Further details of the statistical methods will be provided in the SAP.
Sample Size:	Part 1: The study is designed with co-primary endpoints, ORR, and PFS. In order to maintain an overall 1-sided 10% type I error rate for the study, a Hochberg procedure will be used, such that the trial will be deemed to have met its primary objective if either endpoint is significant at the 1-sided 5% level or if both endpoints are significant at the 1-sided 10% significance level. To ensure that adequate data are available to evaluate the effects of varlitinib on both co-primary endpoints, the DCO for the primary analysis will be the later of 3 months after the last patient in or when 70% of the patients (84 patients) have experienced a PFS event. Based on a minimum of 84 PFS events at the time of the primary analysis, the study would have a minimum of 80% power to detect a true Hazard Ratio (HR) of 0.58 for PFS, based on a 1-sided 5% significance level. Furthermore, if the primary objective of the study is met, the following approach to type I error control will be applied in order to support marketing approval: • The overall type I error rate for marketing approval will be controlled at the two-sided 5% level, using a Hochberg procedure • Using this approach, statistical significance may be claimed if *either* ORR or PFS is significant at the two-sided 2.5% significance level or if *both* ORR and PFS are significant at the two-sided 5% significance level. One hundred and twenty patients will provide approximately 80% power to detect a true difference of 20% in response rate, based on a 2-sided 5% significance level and assuming a 10% response rate for the placebo/capecitabine group and a 30% response rate for the varlitinib/capecitabine group. A total of 84 PFS events provides 80% power to detect a true HR of 0.54, based on a two-sided 5% significance level. Assuming an 8-month non-linear recruitment period, a 2.67-month median PFS for capecitabine alone, and a true HR of 0.54, it is estimated that the DCO for the primary analysis of Part 1 will occur approximately 12 months after the first patient is randomized into the study (first patient in). Part 2: Part 2 is designed with a primary endpoint of OS. Approximately 350 patients will be randomized (1:1) to obtain 247 OS events. If the true OS HR for the comparison of varlitinib + capecitabine vs. placebo + capecitabine is 0.7, the study will have approximately 80% power to demonstrate a statistically significant difference for varlitinib, based on a 2-sided 5% significance level. Assuming a 24-month non-linear recruitment period whereby the proportion of patients recruited by the end of the month i is (i/24)^2, a median OS of 6 months for

	placebo + capecitabine and a true HR of 0.7, it is estimated that 247 OS events will occur approximately 31 months after the first patients is randomized into Part 2.

Table 1: Schedule of Assessments – Safety Lead-in

Assessments	Screening	Study Treatment Period				EOT[m]	Safety Follow up[n]
		Cycle 1			Subsequent Cycles		
	Day -14 to 0	Day 1 (±0 day)	Day 8 (±0 day)	Day 14 (±0 day)	Cycle 2 Day 1, Cycle 3 Day 1, etc. (±5 days)	EOT (+7 days)	28 days post last study medication administration (+7 days)
Informed Consent	X						
Demographics	X						
Medical History	X						
Physical Examination	X	X	X	X	X	X	X
Body Weight	X	X	X	X	X	X	X
Vital Signs [a]	X	X	X	X	X	X	X
12-Lead ECG	X	X [b]	X [b]		X [b]		X
ECOG	X	X	X	X	X	X	X
AE review [c]	X	X	X	X	X	X	X
Prior and Concomitant Medication and Therapy	X	X	X	X	X	X	X
Varlitinib Administration [d]		X [d]	X [d]	X [d]	X		
Capecitabine Administration [e]		X	X		X		
Urine or Serum β-HCG [f]	X					X	
Hematology [g]	X	X	X	X	X	X	X
Clinical Chemistry [g]	X	X	X	X	X	X	X
Urinalysis [g]	X	X	X	X	X	X	
Coagulation [g,h]	X					X	
Serology [i]	X						
Pharmacokinetics [j]		X	X	X			
CT/ MRI	X [l]				X [k]		

Abbreviations: AE = adverse event, β-HCG = beta human chorionic gonadotropin, BID = twice daily, CT = computed tomography, ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, EOT = End of Treatment, MRI = magnetic resonance imaging, PK = pharmacokinetics, SAE = serious adverse event.
Footnotes:

a. Vitals (blood pressure, heart rate, respiratory rate, temperature) are to be collected in a standardized manner in a sitting position after the patient has rested comfortably for 5 minutes.
b. For patients participating in the ECG collection, triplicate 12-Lead ECG using the Central Laboratory-supplied ECG machines will be performed as close as possible and within 25 minutes prior to PK sampling at selected time points as follows: Day 1 and Day 8: 45 minutes pre-dose, 5 minutes pre-dose, 1, 2, 3, 4, 5, 6, 8.5, and 12 hours post-dose. Select time points in this ECG assessments can be waived by the sponsor on a case by case basis. Patients should be rested for at least 10 minutes in a supine position and be resting quietly before the triplicate 12-lead ECG assessment. There should be no significant external stimulation (TV, radio, interaction with other subjects). On Days 1 and 8, concomitant PK samples will be collected immediately after ECG collection at all post-dose time points. At pre-dose time points, PK samples will be collected at 5 minutes and 20 minutes prior to dosing on Cycle 1 Day 1 and Cycle 1 Day 8, respectively.
   Triplicate ECGs will be collected 3 hours post-dose on Day 22 (Cycle 2 Day 1) and onwards every cycle until disease progression. The timing of the ECG acquisition needs to be recorded in the CRF. Refer to the ECG Manual.
c. Adverse event recording will commence from the time of consent and continues until the safety follow-up assessment with the patient.
d. Varlitinib tablets 300 mg administered orally, BID, every day with food. Patients should avoid a high-fat meal. Note: Day 1, Day 8, and Day 14 morning dose can only be administered under supervision of the Investigator (or designee), following collection of pre-dose PK sample and ECG.
e. Capecitabine tablets 1000 mg/m^2 administered orally, BID with food for 14 days from Day 1 to Day 14, followed by 1 week of rest.
f. Serum pregnancy test to be performed at the screening visit for all females except those surgically sterile or 2 years postmenopausal. Serum or urine pregnancy tests will be performed at EOT. Unscheduled serum or urine pregnancy tests may be performed at the Investigator's discretion.
g. Screening clinical laboratory tests (hematology, clinical chemistry, urinalysis and coagulation) must be completed ≤ 21 days prior to Day 1. Screening clinical laboratory tests may be used in lieu of pre-treatment Day 1 tests, if performed within 1 week prior to the first administration of study medications. The clinical laboratory tests obtained as per site standard clinical practice prior to consent is acceptable for screening laboratory tests if it meets the protocol required time window.
h. Coagulation laboratory test will be performed at screening and EOT visit, however investigator may perform coagulation tests at other visits if required based on clinical judgment.
i. Screening viral serology test for HBV and HCV is only needed if there are no existing results within the year prior to screening. Screening viral serology test must be completed ≤ 21 days prior to Day 1. Serology tests include Hepatitis B surface antigen, Hepatitis C Virus antibody and human immunodeficiency virus antibody tests.
j. For patients participating in the PK sampling, blood samples for PK analysis of varlitinib , any relevant varlitinib circulating metabolites, capecitabine and 5-FU (active metabolite of capecitabine) will be collected as follows: Day 1, Day 8 and Day 14: post-dose: 0.5, 1, 2, 3, 4, 5, 6, 8.5, 10, and 12 hours post-dose. Pre-dose PK samples will be collected on Day 1 at 5 minutes pre-dose, Day 8 at 20 minutes pre-dose, and Day 14 at 5 minutes pre-dose. In addition, unscheduled PK will be collected 7 days following dose reduction of varlitinib at any cycle of treatment: up to 5 minutes pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8.5, 10, and 12 hours post-dose if required. Select time points in this PK assessments can be waived by the sponsor on a case by case basis.
k. During study treatment period, CT/MRI imaging of the chest, abdomen, and pelvis images to be performed every 6 weeks (±5 days) from Cycle 1 Day 1. Brain and/or bone lesions may be scanned if applicable. Radiological assessments should continue until EOT visit of the patient is conducted.

l. Baseline CT/MRI of the chest, abdomen, and pelvis images must be performed within 21 days prior to Cycle 1 Day 1, brain and/or bone lesions may be scanned if applicable. The CT/MRI image obtained as per site standard clinical practice prior to consent is acceptable for baseline image if it meets the protocol required CT/MRI image acquisition guidelines and time window.
m. EOT assessments should be performed before the start of a new anti-tumor treatment.
n. If the patient needs to start a new anti-tumor treatment within 28 days post last study medication administration, the safety follow-up assessments should be performed within 1 day before the start of the new anti-tumor treatment.

Table 2: Schedule of Assessments – Part 1 and Part 2

Assessments	Screening	Study Treatment Period							EOT[u]	Safety Follow up [r]	Disease Status FU [s]	Survival FU [t]
		Cycle 1				Cycle 2	Cycle 3	Subsequent cycles				
	Day -14 to 0	Day 1 (±0 day)	Day 8 – Part 1 (±1 day)	Day 8 – Part 2 (±1 day)	Day 15 (±1 day)	Day 1 (± 5 days)	Day 1 (± 5 days)	Cycle 4 Day 1, Cycle 5 Day 1, etc. (± 5 days)	EOT (+7 days)	28 days post last study medication administration (+7 days)	Every 6 weeks (from Cycle 1 Day 1) post EOT until disease progression (± 5 days)	Every 12 Weeks post disease progression (± 7 days)
Informed Consent	X											
Demographics	X											
Medical History	X											
Physical Examination	X	X	X			X	X	X	X	X	X	
Body Weight	X	X	X			X	X	X	X	X	X	
Vital Signs [a]	X	X	X			X	X	X	X	X	X	
12-Lead ECG	X	X [b]	X [b]			X [b]		X [b]		X[b]		
ECOG	X	X	X			X	X	X	X	X	X	
AE review [c]	X	X	X			X	X	X	X	X		
Prior and Concomitant Medication and Therapy	X	X	X			X	X	X	X	X		
Varlitinib Administration [d]		X [d]	X [d]	X	X	X [d]	X	X				
Capecitabine Administration [e]		X	X	X		X	X	X				
Urine or Serum β-HCG [f]	X								X			
Hematology [g]	X	X	X			X	X	X	X			

Assessments	Screening	Study Treatment Period							EOT[u]	Safety Follow up [r]	Disease Status FU [s]	Survival FU [t]
		Cycle 1				Cycle 2	Cycle 3	Subsequent cycles				
	Day -14 to 0	Day 1 (±0 day)	Day 8 – Part 1 (±1 day)	Day 8 – Part 2 (±1 day)	Day 15 (±1 day)	Day 1 (± 5 days)	Day 1 (± 5 days)	Cycle 4 Day 1, Cycle 5 Day 1, etc. (± 5 days)	EOT (+7 days)	28 days post last study medication administration (+7 days)	Every 6 weeks (from Cycle 1 Day 1) post EOT until disease progression (± 5 days)	Every 12 Weeks post disease progression (± 7 days)
Clinical Chemistry [g]	X	X	X			X	X	X	X			
Liver Function Test [q]				X	X							
Urinalysis [g]	X	X	X			X	X	X	X			
Coagulation [g,h]	X								X			
Serology [i]	X											
CA19.9 and CEA [j]	X						X	X[j]	X[j]			
Collection of tumor tissue [k]	X											
Biopsy [l]	X											
Pharmacokinetics [m]		X	X			X				X		
Biomarker Sampling [n]	X						X					
CT/ MRI [o]	X [p]						X	X[o]			X	
Survival status contact												X

Abbreviations: AE = adverse event, β-HCG = beta human chorionic gonadotropin, CA19.9 = cancer antigen 19.9, CEA = carcinoembryonic antigen, CT = computed tomography, ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, EOT = End of Treatment, MRI = magnetic resonance imaging, SAE = serious adverse event.

Footnotes:

a. Vitals (blood pressure, heart rate, respiratory rate, temperature) to be collected in a standardized manner in a sitting position after the patient has rested comfortably for 5 minutes.
b. Part 1: Triplicate 12-Lead ECG using the Core Laboratory-supplied ECG machines will be performed as close as possible and within 25 minutes prior to PK sampling at selected time points on
   - Cycle 1 Day 1: 45 minutes pre-dose, 5 minute pre-dose, 1.5, 3, 5, and 8 hours post-dose. Concomitant PK samples will be collected immediately after the ECG collections, except for 45 minutes pre-dose time point where no PK sample will be collected.
   - Cycle 1 Day 8: 45 minutes pre-dose, 5 minutes pre-dose, 1.5, 3, 5, and 8 hours post-dose. Concomitant PK samples will be collected immediately after the ECG collections, except for the 45 minutes and 5 minutes pre-dose time points. One pre-dose PK sample will be collected on Cycle 1 Day 8 at the 20 minutes pre-dose time point.
   - End of Study after full drug washout (at 28 days after the last dose) a set of triplicate ECGs will be collected 3 hours after a light snack. A concomitant PK sample will be collected immediately after the ECG collection.
   - In addition, triplicate safety ECGs will be collected 3 hours post-dose on Day 22 (Cycle 2 Day 1), Day 64 (Cycle 4 Day 1) and every 2 cycles until disease progression. These ECGs will not be analyzed by the Core ECG Laboratory.

   Patients should be rested for at least 10 minutes in a supine position and be resting quietly before the triplicate 12-Lead ECG assessment. There should be no significant external stimulation (TV, radio, interaction with other subjects).

   Part 2: Triplicate safety ECGs will be collected at screening, baseline (before a snack), and 3 hours post-dose on Day 22 (Cycle 2 Day 1) and Day 64 (Cycle 4 Day 1) and every 2 cycles while the subject remains in the study. These ECGs will not be analyzed by the Core ECG Laboratory but assessed by the investigators.
c. Adverse event recording will commence from the time of consent and continues until the safety follow-up assessment with the patient.
d. Varlitinib tablets 300 mg administered orally, BID, every day with food. Patients should avoid a high-fat meal. Note: Cycle 1 Day 1, Cycle 1 Day 8 (Part 1 only), and Cycle 2 Day 1 morning dose can only be administered under supervision of the Investigator (or designee), following collection of pre-dose PK sample and ECG.
e. Capecitabine tablets 1000 mg/m^2 administered orally, BID with food for 14 days from Day 1 to Day 14, followed by 1 week of rest.
f. Serum pregnancy test to be performed at the screening visit for all females except those surgically sterile or 2 years postmenopausal. Serum or urine pregnancy tests will be performed at EOT. Unscheduled serum or urine pregnancy tests will be performed at the Investigator's discretion.
g. Screening clinical laboratory tests (hematology, clinical chemistry, urinalysis and coagulation) must be completed ≤ 21 days prior to Day 1. Screening clinical laboratory tests may be used in lieu of pre-treatment Day 1 tests, if performed within 1 week prior to the first administration of study medications. The clinical laboratory tests obtained as per site standard clinical practice prior to consent is acceptable for screening laboratory tests if it meets the protocol required time window. Liver function testing is included in the Clinical Chemistry testing.
h. Coagulation laboratory test will be performed at screening and EOT visit, however investigator may perform coagulation tests at other visits if required based on clinical judgment.
i. Screening viral serology test for HBV and HCV is only needed if there are no existing results within the year prior to screening. Screening viral serology test must be completed ≤ 21 days prior to Day 1. Serology tests include Hepatitis B surface antigen, Hepatitis C Virus antibody and human immunodeficiency virus antibody tests.

j. During the study treatment period, blood is to be collected for the analysis of CA19.9 and CEA at every 6 weeks (±5 days) from Cycle 1 Day 1 together with CT/MRI. The final collection of blood for these analyses should occur at EOT. If the reason for EOT is due to radiological disease progressions and CA19.9/CEA have already been assessed with the most recent scans, then CA19.9/CEA at EOT can be omitted.
k. Archival paraffin-embedded tumor tissues will be collected during screening for future analysis (the minimum archival tumor tissue to be collected is 19 unstained slides of 5 microns).
l. Biopsy will be performed during screening for those patients who did not have enough archival tumor tissue if the patient has provided the optional tumor tissue consent.
m. Blood samples for PK analysis of varlitinib and any relevant circulating metabolites will be collected as follows:
Part 1 (All Patients):
    - Cycle 1 Day 1: 5 minutes pre-dose, 1.5, 3, 5, and 8 hours post-dose. PK samples will be collected immediately after the ECG collections.
    - Cycle 1 Day 8: 20 minutes pre-dose, 1.5, 3, 5, and 8 hours post-dose. PK samples will be collected immediately after the ECG collections.
    - End of study after full drug washout: 28 days after last dose at the patient's safety follow-up visit. PK samples will be collected within 25 minutes after ECG evaluation.

    Part 2:
    Sparse plasma sampling will be conducted for the population PK evaluation by using nonlinear mixed effects models on:
    - Cycle 1 Day 1: 5 minutes pre-dose, 1-3 hours post-dose, 3-5 hours post-dose, and 5-8 hours post-dose
    - Cycle 2 Day 1: 20 minutes pre-dose, 1-3 hours post-dose, 3-5 hours post-dose, and 5-8 hours post-dose.

    Part 1 & Part 2: In addition, unscheduled PK samples will be collected at least 7 days following dose reduction of varlitinib at any cycle of treatment: up to 5 minutes pre-dose and 3-5 hours post-dose.
n. Blood samples for potential retrospective analysis of potential biomarkers will be collected at baseline and Cycle 3 Day 1
o. CT/MRI imaging of the chest, abdomen, and pelvis images to be performed every 6 weeks (±5 days) from Cycle 1 Day 1. Brain and/or bone lesions may be scanned if applicable. Radiological assessments should continue until the patient experiences disease progression, regardless of whether the patient discontinues randomized therapy or starts a subsequent anti-cancer therapy.
p. Baseline CT/MRI of the chest, abdomen, and pelvis images must be performed within 21 days prior to Cycle 1 Day 1, brain and/or bone lesions may be scanned if applicable. The CT/MRI image obtained as per site standard clinical practice prior to consent is acceptable for baseline image if it meets the protocol required CT/MRI image acquisition guidelines and time window.
q. Additional weekly liver function test (AST, ALT, alkaline phosphatase, gamma glutamyl transferase, total bilirubin, direct bilirubin) will also be performed for all patients on Cycle 1 Day 8 and Cycle 1 Day 15.
r. No other additional study-related activities or assessments are mandated during follow-up visit; however, patient data available from the assessments done as part of their routine follow-up visits will be collected by the sponsor. If the patient needs to start a new anti-tumor treatment within 28 days post last study medication administration, the safety follow-up assessments should be performed within 1 day before the start of a new anti-tumor treatment.
s. Disease status follow-up will be performed post EOT every 6 weeks from Cycle 1 Day 1, regardless of timing of EOT.
t. Survival follow-up by either telephone or clinic visit will be performed every 12 weeks post EOT and PD until death to find out the survival status, new chemotherapy or biological treatments and the outcome of any ongoing adverse events.
u. EOT assessments should be performed before the start of new anti-tumor treatment.

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2.1 List of In-text Tables

2.2 List of In-text Figures

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
AKT	protein kinase B
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{τ}	area under the plasma concentration-time curve during a dosage interval (τ)
BID	twice daily
BMI	body mass index
BP	blood pressure
BTC	biliary tract cancer
CCA	cholangiocarcinoma
CI	confidence interval
CL	observed systemic plasma clearance
C_{max}	maximum concentration
CTCAE	common terminology criteria for adverse events
C_{trough}	Trough plasma concentration
CRF	case report form
CRO	contract research organization
DCO	data cut-off
DCR	disease control rate
DoR	duration of response
DSMB	data safety monitoring board
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EFR	evaluable for response
EGFR	epidermal growth factor receptor
5'-DFCR	5'-deoxy-5-fluorocytidine
5'-DFUR	5'-deoxy-5-fluorouridine
EOT	end of treatment

5-FU	5-fluorouracil
FAS	full analysis set
FBAL	α-fluoro-β-alanine
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HER	human epidermal growth factor receptor
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICR	independent central review
IEC	independent ethics committee
IRB	institutional review board
KM	Kaplan Meier
LLN	Lower Limit of Normal
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NLME	nonlinear mixed effects model
ORR	objective response rate
OS	overall survival
PFS	Progression-free survival
PK	pharmacokinetic
PP	Per protocol
PR	partial response
QTc	corrected QT interval
QTcF	corrected QT interval (Fridericia's formula)
Rac AUC	Accumulation ratio calculated from $AUC_{\tau,ss}$ and AUC_{τ} after single dosing
Rac C_{max}	Accumulation ratio calculated from $C_{max,ss}$ and C_{max} after single dosing
RECIST	Response Evaluation Criteria in Solid Tumours
ROW	rest of world

RTSM	Randomization and Trial Supply Management
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SLI	Safety lead-in
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal elimination half-life
TID	three times a day
T_{max}	time of maximum concentration
ULN	upper limit of normal
US	United States
V_z	apparent volume of distribution during terminal phase
V_{ss}	steady-state volume of distribution

3 INTRODUCTION

Varlitinib (also known as ASLAN001) is a small-molecule, adenosine triphosphate competitive inhibitor of the tyrosine kinases-epidermal growth factor receptor (EGFR), human epidermal growth factor receptor (HER)2, and HER4, developed by Array BioPharma.

ASLAN Pharmaceuticals Pte. Ltd. (ASLAN) has in-licensed varlitinib (ASLAN001) as of July 2011, and is responsible for future clinical development of the molecule. In August 2015, varlitinib was granted orphan-drug designation status for the treatment of cholangiocarcinoma by the United States (US) Food and Drug Administration (FDA), Office of Orphan Products Development.

3.1 Background

Biliary tract cancers (BTCs) are heterogeneous and highly lethal malignancies including a spectrum of invasive carcinomas arising in the gallbladder and bile ducts (intrahepatic and extrahepatic), and variably, ampullary carcinoma. These tumors are very uncommon, representing less than 1% of all cancers in the developed countries. Approximately 1200 new cases in the United Kingdom and 9000 new cases in the US are diagnosed per year, although the incidence is increasing, perhaps related to gallstone disease. Despite this relative rarity, these tumors present a significant therapeutic challenge as most patients are often diagnosed at an advanced stage when surgical resection is not feasible and treatment options are limited. The 5-year overall survival rates are 5% to 10% for gallbladder cancers and 10% to 40% for cholangiocarcinomas.[1,2,3]

Surgical resection with negative margins or liver transplantation remains the potential therapy for cure, but only for the minority of patients whose tumors appear resectable on staging assessments. However, recurrence occurs frequently for this resectable subset, with more local than distant relapse. Orthotopic liver transplantation is also a potential avenue for cure in patients with unresectable perihilar or intrahepatic cholangiocarcinoma. The benefit of neoadjuvant chemoradiation in quality of resection as well as survival is limited. Thus, systemic therapy, largely relied on cytotoxic chemotherapy, remains a necessary component of treatment both for recurrent disease or for tumors advanced at diagnosis.[2] Currently, the FDA approved agents that are used to treat cholangiocarcinoma include gemcitabine, capecitabine, cisplatin, oxaliplatin, fluoropyrimidines (including 5-Fluorouracil [5-FU]), or a combination of these. However, it is important to note that none of these agents is FDA approved primarily for use in biliary tract cancers.[4]

Historically, there has been no standard treatment for advanced or metastatic BTC. A randomized Phase 2 study was conducted in 410 patients with locally advanced or metastatic cholangiocarcinoma, gallbladder cancer and ampullary cancer to receive cisplatin (25 mg/m^2) followed by gemcitabine (1000 mg/m^2) on Days 1 and 8 every 21 days or gemcitabine (1000 mg/m^2) on Days 1, 8, and 15 every 28 days. A significant benefit in both response rate and progression free survival (PFS) was seen favoring the gemcitabine/cisplatin arm. Furthermore, median overall survival (OS) was 11.7 months in the gemcitabine/cisplatin group compared with 8.1 months in the gemcitabine-only

group (hazard ratio 0.64; 95% CI, 0.52–0.80, $p < 0.001$), with no increase in adverse events (AEs) for the combination arm when compared with the single-agent.

While cytotoxic chemotherapeutic agents are useful in the treatment of biliary tract cancers, the magnitude of their beneficial effects is less than desired. Targeted therapies based on the understanding of the molecular basis of tumors are being investigated in biliary tract cancers with some promising results. Targeted therapies, perhaps in combination with cytotoxic agents, may be the most promising advancement in this tumor type.[2]

The human EGFR family consists of four members: HER1 (EGFR), HER2 (c-erbB-2), HER3 (c-erbB-3) and HER4 (c-erbB-4). Epidermal growth factor receptor, HER2, and HER4 are single-pass transmembrane glycoprotein receptors, members of the type I receptor tyrosine kinase family. Upon ligand binding, their activation induces the homo- or hetero-dimerization and subsequent phosphorylation of intracellular tyrosines, which lead to both cell proliferation and survival and therefore cancer development and progression. Aberrations in EGFR family members play a role in the development and progression of many human cancers.[5,6,7,8]

Epidermal growth factor receptor is variably expressed in the majority of biliary tract cancers, with expression occurring nearly ubiquitously in intrahepatic cholangiocarcinomas, and to a slightly lesser extent in the other tumor types. Human epidermal growth factor 2 is overexpressed in only a minority of biliary tract cancers, but preclinical experiments have shown that simultaneous blockade of EGFR and HER2 by lapatinib leads to growth inhibition of an orthotopic rat model of intrahepatic cholangiocarcinoma if administered early.[2,9] Both EGFR and HER2 inhibitors have demonstrated clinical efficacy in cancer treatment. Thus, a simultaneous inhibition of EGFR, HER2, and HER4 represents a new therapeutic approach for broadly targeting different tumor types that may be more effective than selective inhibition of each receptor.

3.2 Varlitinib

Varlitinib is a potent, small-molecule, adenosine triphosphate-competitive inhibitor of the receptor tyrosine kinases EGFR, HER2, and HER4. ASLAN believes that varlitinib is a compound that may be beneficial to patients with cancer by simultaneous inhibition of these receptors.

Full details of nonclinical and clinical studies conducted to date are provided in the Investigator's Brochure (IB).[10] The following sections provide a summary of varlitinib studies conducted.

3.2.1 Nonclinical Studies

Nonclinical studies including *in vivo* pharmacology studies, pharmacokinetic studies, toxicokinetic studies, absorption, distribution, metabolism and excretion studies, and toxicology studies have been conducted with varlitinib.

Numerous pharmacology studies have demonstrated the activity of varlitinib in tumor-bearing animal models of breast cancer, non-small cell lung cancer, gastric cancer, ovarian cancer, and epidermoid cancer. Significant inhibition of tumor growth (> 70%) was seen with twice daily (BID) doses of 100 mg/kg and once daily doses of 200 mg/kg in the EGFR-driven A431 tumor xenograft model of epidermoid carcinoma.

Toxicity studies have been conducted in Sprague-Dawley rats (acute and repeat dose) and cynomolgus monkeys (repeat dose). The main observed adverse effects in both species were gastrointestinal disturbances, soft stools, weight loss, mild clinical chemistry, and hematology changes and partially reversible histopathological alterations.

The administration of varlitinib at doses up to 60 mg/kg was tolerated in most animals in an extensive panel of safety studies. The overall conclusion from safety studies is that varlitinib has an acceptable safety profile for administration in human cancer patients at the proposed doses.

Details of the full varlitinib nonclinical program are presented in the IB.[10]

3.2.2 Clinical Studies

Varlitinib has been administered as a single agent and in combination with other agents in 5 completed Phase 1 studies and 1 completed Phase 2A study and is currently being administered in 7 on-going studies. Patients with metastatic gastric cancer, gastro-esophageal tumors, breast cancer, and biliary tract cancer have been being evaluated. As of 31 December 2016, a total of 345 patients with solid tumors had been administered varlitinib at total daily doses ranging from 50 mg to 1200 mg.

Completed single-agent studies of varlitinib include a Phase 1 dose-escalation and expansion study of the ditosylate salt capsule (Clinical Study ARRY-0501), a Phase 1 dose-escalation study of the free base tablet (Clinical Study ARRAY-543-103), and a Phase 2a study of the tolerability and biological activity of the free base tablet (Clinical Study ASLAN001-001). Completed combination studies of varlitinib as a free base tablet include a Phase 1 dose-escalation combination study with docetaxel (Clinical Study ARRAY-543-104), a Phase 1 dose-escalation combination study with capecitabine (Clinical Study ARRAY-543-204), and a Phase 1 dose-escalation combination study with gemcitabine (Clinical Study ARRAY-543-206). The maximum tolerated dose (MTD) has been determined for varlitinib as a single agent and in combination with 3 separate standard chemotherapies (docetaxel, capecitabine, and gemcitabine) in patients with advanced solid tumors. Ongoing Phase 2 studies are being conducted in patients with BTC, metastatic breast cancer, and gastric cancer.

Evaluation of the efficacy of varlitinib in the clinical studies conducted to date has demonstrated that partial response (PR) or stable disease (SD), as defined by the Response Evaluation Criteria in Solid Tumours (RECIST) has been observed with varlitinib in each clinical study to date. In one study (ARRAY-543-103), the incidence of stable disease was higher in the varlitinib 500 mg BID cohort than the varlitinib 300 mg or 400 mg BID cohorts.

There was a trend for patients with HER2-positive tumors to have an increased rate of stable disease compared to patients with HER2-negative tumors. Conversely, there was a trend for patients with EGFR-positive tumors to have a decreased rate of stable disease compared with to patients with EGFR-negative tumors (ARRAY-543-0501).

Adverse events of diarrhea, nausea, and vomiting have been reported frequently across all studies conducted with varlitinib. The time of onset of these AEs has been variable with the majority of episodes being managed with standard anti-emetic and anti-diarrheal medications. Dermatological AEs have been reported during varlitinib therapy including rash, erythematous rash, papular rash, macular rash, maculopapular rash, exfoliative rash, skin exfoliation, dermatitis acneiform, and acne. If symptoms are not adequately controlled with symptomatic treatment, a dose holiday (either with or without subsequent dose reduction) may be required.

Elevation in serum liver transaminases (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) and cases of hyperbilirubinemia have been observed in some patients receiving varlitinib. Levels of ALT, AST, conjugated and total blood bilirubin as well as signs and symptoms of liver toxicity should be monitored during varlitinib treatment. Cases of increased serum creatinine have been observed particularly when varlitinib is administered with platinum-based chemotherapies. Appropriate monitoring of renal function is recommended.

Prolongation of the corrected QT interval (QTc) by > 60 milliseconds (msec) from baseline has been observed in 2 patients. Two patients in Study ARRAY-543-204 experienced clinically significant QT prolongations with one of the patients having multiple cardiopulmonary complications at baseline and remaining on treatment with verapamil and digoxin, both of which could have interfered with QTc measurements during the study. The QTc prolongation in the second patient was assessed as not related to study treatment and the patient was withdrawn from the study due to a major protocol violation. *In vitro* studies have shown that therapeutically active concentrations of varlitinib are 1200- to 1625-fold lower than those likely to produce any change in cardiac conduction. Therefore, it is unclear if the existing data implicate varlitinib in any way in the observed QTc prolongation events.

Details of the full varlitinib clinical program are presented in the IB.[10]

3.2.3 Known or Potential Risks of Varlitinib

Varlitinib has demonstrated an acceptable safety profile in nonclinical toxicology studies and in the completed Phase 1 and Phase 2A studies in humans. However, as with any new investigational drug, unexpected AEs may occur with the use of varlitinib. The following is a summary of potential risks; additional details are presented in the IB[10]:

- Varlitinib must not be administered to pregnant or nursing women
- Varlitinib exposure is negatively influenced by co-administration of proton pump inhibitors, H2 antagonists, and co-medications that increase gastric pH
- Varlitinib may cause a drug-drug interaction with other medications that are CYP3A4, CYP2C8, or CYP2C9 inducers, inhibitors, or substrates. Due to the potential for drug interactions based on in vitro screens, concomitant use of

moderate CYP3A4, CYP2C8, CYP2C9, and P-gp inducers or inhibitors will be recorded during the entire clinical study
- Signs of gastrointestinal side effects (diarrhea, nausea, and vomiting) should be monitored in patients receiving varlitinib. However, prophylactic anti-emetics are usually not required with varlitinib administration
- ALT, AST, and bilirubin along with signs or symptoms of liver toxicity should be monitored during varlitinib treatment

3.2.4 Known or Potential Risks of Capecitabine

In this study, varlitinib will be co-administered with capecitabine. Refer to the XELODA® (capecitabine) prescribing information leaflet[12] for known and potential risks following administration of capecitabine.

3.3 Rationale for the Study

Biliary tract cancer (BTC) is a therapy-refractory cancer with very limited treatment alternatives. First-line therapy is often a combination of gemcitabine and cisplatin, as recommended in the National Comprehensive Cancer Network (NCCN) guidelines. A standard second-line therapy for BTC has not been established and no drug is currently approved in the US for this indication. In the ABC-02 study, approximately 15% of the patients were treated with 5-FU-based chemo¬therapy as second-line treatment after progression from the gemcitabine/cisplatin (GC) regimen, with a median OS of 11.2 months (Valle et al. 2010). There is data suggesting that the 5-FU principle may be useful in BTC, such as the S-1 data from Japan and small studies with capecitabine in BTC.

However, although the efficacy was demonstrated in phase II studies in a small number of patients and the second-line chemotherapies are considered for patients who can receive chemotherapies, sufficient evidence has not been established. In addition, no clinical studies have been conducted to directly compare the second-line chemotherapies with no treatment (supportive therapy) and it is necessary to investigate whether the second-line chemotherapies contribute to the extension of survival. The NCCN recommends monotherapy or combination of the following agents indicated for unresectable biliary cancer: gemcitabine, capecitabine, cisplatin, oxaliplatin, and fluoropyrimidine (including 5-FU). These agents, however, are not prioritized agents for biliary cancer approved by the FDA.

The second-line agents for biliary cancer differ in each country, but capecitabine is one of the common options at the present. Capecitabine is an oral fluorouracil prodrug that undergoes enzyme conversion to 5-FU in the body and is used for advanced biliary cancer off-label in accordance with the NCCN guideline, because of the limited therapies for advanced biliary cancer. From the above, ASLAN considers that varlitinib in combination with capecitabine can provide even more benefits to patients with biliary tract cancer.

Varlitinib has demonstrated tumor shrinkage responses and durable disease stabilization in BTC in ongoing Phase IB safety and tolerability studies in Singapore (ASLAN001-002SG) and Taiwan (ASLAN001-002).

The potential efficacy of varlitinib in BTC is also supported by nonclinical studies which have demonstrated dysregulated HER1 and HER2 activity in this tumor type and support the hypothesis that HER receptors are driving BTC tumor proliferation and survival. In terms of drug metabolism, varlitinib is cleared via the biliary tract and therefore drug concentrations should be high at the primary tumor site.

Furthermore, results from an ongoing study in trastuzumab-failed metastatic breast cancer (ASLAN001-003) where 400 mg BID varlitinib in combination with capecitabine demonstrate that the combination of varlitinib and capecitabine has anti-tumor activity, is well-tolerated and would be a rational combination in multiple malignancies, including BTC.

Second-line BTC remains an area of high unmet medical need. To date, no randomized clinical studies have demonstrated statistically significant improvements in any efficacy parameters. Most of the studies used small, single arm designs. Thus a study with a double-blind, placebo-controlled, randomized design has the potential to provide robust, evidence of efficacy in second-line BTC. Primary efficacy endpoints that will be used to evaluate efficacy in the study include Objective Response Rate (ORR) and PFS for Part 1 of the study and OS for Part 2 of the study. These are well known endpoints for oncology studies and have been used to support health authority decisions on drug approvability. See Section 5.2 for a further discussion of the study design.

4 STUDY OBJECTIVES

4.1 Primary Objective

The primary objectives of the study are:

Safety lead-in:

- To assess the safety and tolerability of varlitinib 300 mg BID (every day), in combination with capecitabine 1000 mg/m^2 (BID for 14 days followed by a 7-day rest) as measured by incidence of AEs, and changes from baseline in safety parameters.

Part 1:

- To assess the efficacy of varlitinib in combination with capecitabine as measured by co-primary endpoints of ORR and PFS, both assessed by an Independent Central Review (ICR).

Part 2:

- To assess the efficacy of varlitinib in combination with capecitabine as measured by OS.

4.2 Secondary Objective(s)

The secondary objectives of the study are:

Safety lead-in:

1. To evaluate the pharmacokinetics (PK) of varlitinib (and any relevant circulating metabolites) and capecitabine (and its active metabolite 5-FU) when given in combination
2. To evaluate the effect of varlitinib on QT/QTc
3. To evaluate the efficacy of varlitinib in combination with capecitabine, as measured by ORR, duration of response (DoR), and disease control rate (DCR), all based on site assessment

Part 1:

1. To evaluate the efficacy of varlitinib in combination with capecitabine, as measured by DoR, and DCR as assessed by ICR, and OS and ORR as assessed by the site
2. To assess the safety and tolerability of varlitinib when combined with capecitabine
3. To explore exposure-response relationships for varlitinib (and any relevant circulating metabolites) for measures of efficacy, safety, and pharmacological responses
4. To examine the effects of varlitinib, when added to capecitabine on electrocardiogram (ECG) parameters including QTcF, QTcB, HR, PR and QRS

Part 2:

1. To evaluate the efficacy of varlitinib in combination with capecitabine, as measured by ORR, DoR, DCR and PFS, all based on site assessment
2. To assess the safety and tolerability of varlitinib when combined with capecitabine
3. To explore exposure-response relationships for varlitinib (and any relevant circulating metabolites) for measures of efficacy, safety, and pharmacological responses via sparse PK sampling and population PK analyses

4.3 Exploratory Objectives

The exploratory objectives of the study are:

Part 1:

1. To explore the role of HER family of receptor status as a predictor of benefit to varlitinib
2. To explore possible relationships between HER family and downstream signaling protein and phospho-protein expression levels and clinical outcomes
3. To explore possible relationships between gene mutational status and clinical outcomes

Part 2:

If a relationship is found between biomarker(s) expression and clinical outcomes in Part 1 of the study, the biomarker(s) could be prospectively evaluated in Part 2 of the study.

5 INVESTIGATIONAL PLAN

5.1 Overall Study Design and Plan: Description

5.1.1 Study Design

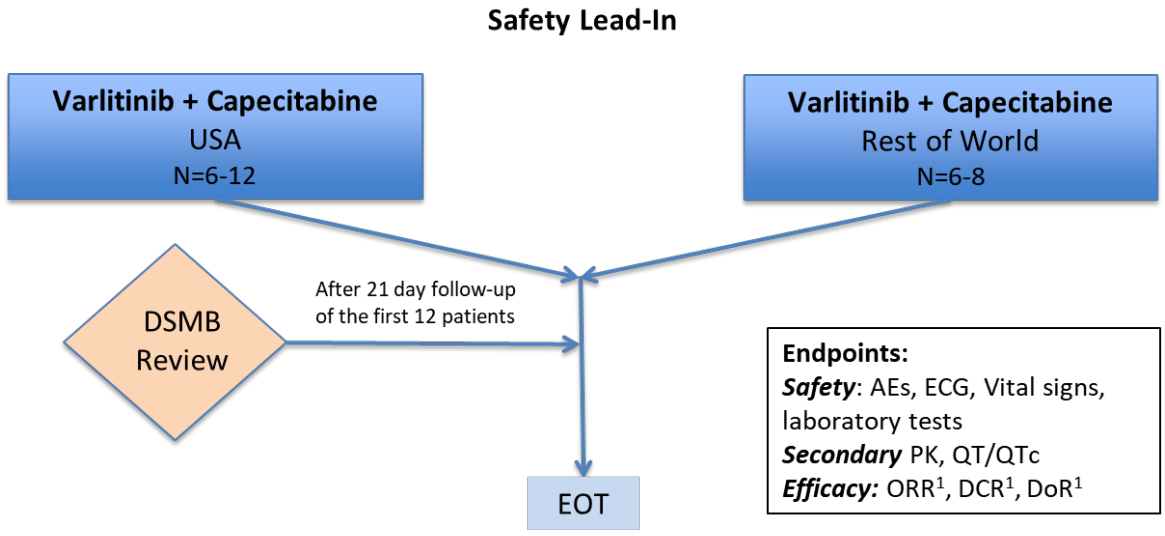
This study is designed as a multicenter, double-blind, randomized, placebo-controlled study of varlitinib plus capecitabine versus placebo plus capecitabine in patients with advanced or metastatic BTC as second-line systemic therapy.

Safety Lead-in:

This study will commence initially with a Safety lead-in group (Figure 1). This part of the study is a single arm, open-label design to assess the safety of varlitinib (300 mg administered BID every day) plus capecitabine (1000 mg/m^2 administered BID every day for 14 days, followed by a 7-day rest period) in a small set of patients (12 to 20 patients) with 12 patients completing the PK and ECG evaluations. Treatment will continue until disease progression, development of unacceptable toxicity, withdrawal of consent, or death.

A data safety monitoring board (DSMB) meeting will occur after the first 12 patients in the Safety lead-in who have completed 21 days of follow-up in order to review the safety and tolerability data prior to commencement of Part 1 of the study.

Figure 1: Safety Lead-in Study Design



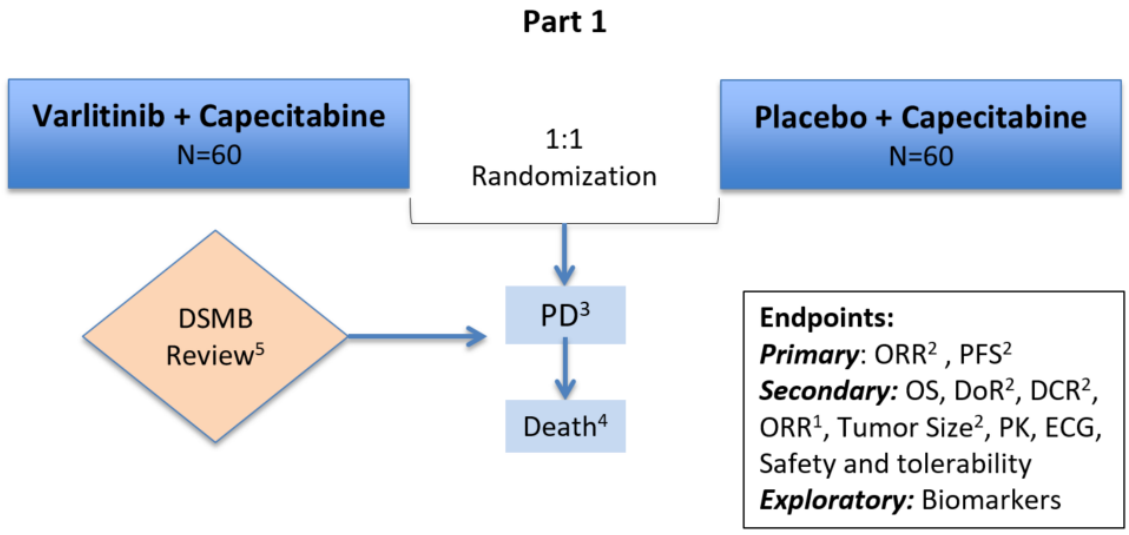
1. As assessed by site review

Abbreviations: AE = adverse event, DCR = disease control rate, DoR = duration of response, DSMB = data safety monitoring board, ECG = electrocardiogram, N = number of patients, ORR = objective response rate, PK = pharmacokinetics, QT/QTc = QT interval / corrected QT interval, USA = United States of America.

Part 1:

Part 1 of the study is designed as a double-blind, randomized, placebo-controlled study to assess the efficacy and safety of varlitinib plus capecitabine in comparison with placebo plus capecitabine in approximately 120 patients (Figure 2). Eligible patients will be randomized to varlitinib or placebo (300 mg administered BID every day) plus capecitabine (1000 mg/m^2 administered BID every day for 14 days, followed by a 7-day rest period). Treatment will continue until disease progression, development of unacceptable toxicity, withdrawal of consent, or death. A DSMB will meet at a selected time point (to be confirmed) during Part 1 for review of safety data.

Figure 2: Part 1 Study Design



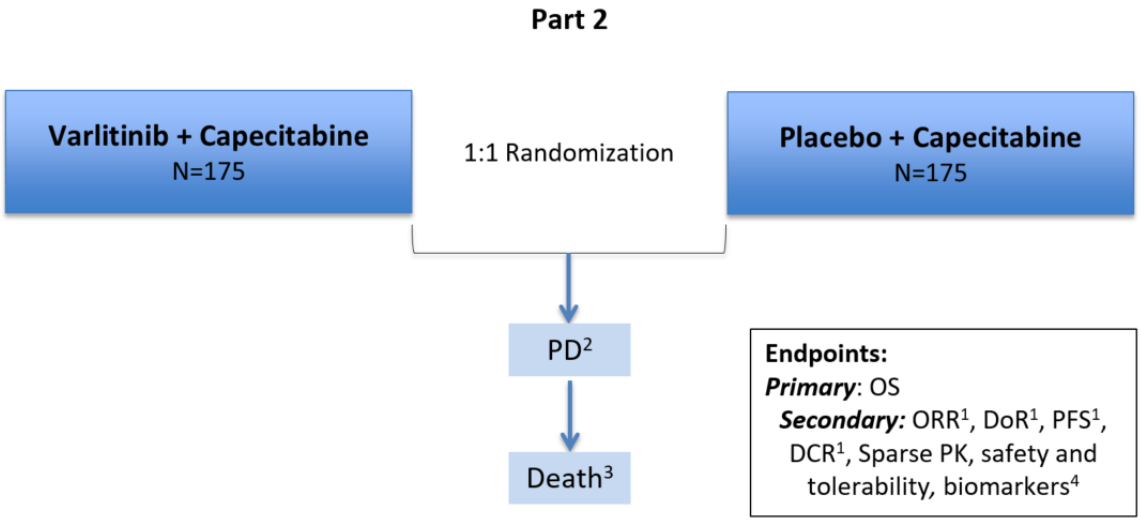
1. As assessed by site review
2. As assessed by Independent Central Review
3. Tumor response will be assessed every 6 weeks until disease progression
4. Following disease progression, patients in Part 1 will be followed for survival every 12 weeks until the DCO for the primary analysis of Part 2
5. An additional DSMB review on safety data will be performed during Part 1, as described in DSMB charter

Abbreviations: N = number of patients, DCR = disease control rate, DoR = duration of response, DSMB = data safety monitoring board, ECG = Electrocardiogram, OS = overall survival, PD = progressive disease, PFS = progression-free survival, PK = pharmacokinetics.

Part 2:

Part 2 of the study is designed as double-blind, randomized, placebo-controlled study to confirm the efficacy of varlitinib (300 mg administered BID) plus capecitabine (1000 mg/m^2 administered BID for 14 days out of 21 days) compared to capecitabine in approximately 350 patients (Figure 3). Part 2 will follow the same design and treatment schedule as Part 1. This part of the study will commence following review of Part 1 results.

Figure 3: Part 2 Study Design



1. As assessed by site review
2. Tumor response will be assessed every 6 weeks until disease progression
3. Following disease progression, patients in Part 2 will be followed for survival every 12 weeks until the final overall survival analysis
4. Depending on the results of the exploratory biomarker analysis in Part 1, biomarkers could be prospectively evaluated in Part 2

Abbreviations: N = number of patients, DCR = disease control rate, DoR = duration of response, OS = overall survival, PD = progressive disease, PFS = progression-free survival, PK = pharmacokinetics.

5.2 Discussion of Study Design

To date, no randomized clinical studies in second-line BTC have demonstrated statistically significant improvements in any efficacy parameters. Historically, clinical studies in second-line BTC have been conducted using small, single arm designs. Consequently, the results of these studies can be difficult to interpret and compare, due to the intrinsic bias known to afflict single arm designs.

The proposed study has been designed to provide robust, unequivocal evidence of efficacy in second-line BTC. For that reason, a randomized, double-blind, placebo-controlled design has been selected to definitively quantify the contribution of varlitinib, above and beyond the background chemotherapy agent, capecitabine.

ASLAN001-009 is designed to provide sufficient data on the efficacy and safety of varlitinib in combination with capecitabine in patients with advanced or metastatic BTC

who have progressed after one line of systemic therapy in order to support a decision on its approvability for marketing. The control will be capecitabine plus placebo.

The proposed dose of varlitinib is 300 mg BID. The MTD of varlitinib in combination with capecitabine 1000 mg/m^2 BID was determined to be 400 mg BID based on previous studies of the combination therapy (ARRAY-543-204). Considering that patients with BTC who have failed one line of systemic therapy are usually frail with multiple co-morbidities, the dose of varlitinib selected for this study is 300 mg BID in combination with capecitabine.

The dosing schedule of capecitabine selected for this study will be capecitabine at 1000 mg/m^2 BID for 2 weeks followed by a 1-week rest period in 3-week cycles. The dosage, PK, and safety of capecitabine (1000 mg/m^2 BID, Day 1 to Day 14, followed by a 7-day rest period) have been established in the ARRAY-543-204 study. This dose of capecitabine has been successfully used with varlitinib in patients with advanced metastatic breast cancer (ASLAN001-003) and in a study (NCT00078572) where capecitabine was used in combination with lapatinib in metastatic breast cancer.[11,13]

Study ASLAN001-009 is anticipated to be conducted worldwide with approximately 20% of the patients from US sites.

This study will commence initially with a Safety lead-in group designed as a single arm, open label study to assess the safety of varlitinib plus capecitabine in a small set of patients (12 to 20) prior to commencing Part 1 in a larger study population (n=120). A DSMB will review safety data on 2 occasions (refer to Section 7.2) to monitor the safety of patients. Part 2 (n=350) of the study will not commence until the results of Part 1 have been evaluated.

Part 1 of the study includes co-primary endpoints of ORR and PFS determined via central review. Overall survival is the primary endpoint in Part 2 of the study. These are well known endpoints for oncology studies and have been used to support health authority decisions on drug approvability.

In Part 1 of the study, for the purpose of marketing approval, a Hochberg procedure will be used to control the overall type I error rate associated with the co-primary endpoints, ORR and PFS, at the two-sided 5% level. Using this approach, statistical significance can be declared if *either* ORR or PFS is significant at the two-sided 2.5% level, or if *both* endpoints are significant at the two-sided 5% significance level. For significance at the 2-sided 5% level, the study has approximately 80% power to detect a 20% difference in ORR, assuming a 10% response rate for the control arm. Similarly, for significance at the two-sided 5% level, 84 PFS events would provide approximately 80% power to detect a true HR of 0.54 (approximately an 84% prolongation in PFS). If statistical significance is demonstrated, ASLAN believes that these effect sizes represent a clinically meaningful improvement in efficacy relative to the current care options. This improvement would represent a step-change in the treatment options for patients with second line BTC. To enable a further illustration of the clinical benefit realized through the improvement in ORR, DoR will be included as a secondary endpoint in the study and will help characterize the durability of the observed responses. All radiological data collected in

the Part 1 of the study will be assessed via an ICR of the imaging data thus eliminating the potential bias that can arise from site evaluations.

Data from the Safety lead-in, Part 1 and Part 2 will be evaluated separately for safety and efficacy. Patients whose data contributed to the Part 1 analysis will not be included in the Part 2 analysis.

5.3 Selection of Study Population

5.3.1 Number of Planned Patients

Safety lead-in:

A total of 12 to 20 eligible patients will be enrolled to receive varlitinib plus capecitabine.

United States: 6 to 12 eligible patients are expected to be enrolled from the United States.

Rest of the World: An additional 6 to 8 eligible patients will be enrolled from the rest of the world.

Patients in this group will be replaced if investigational product compliance is < 85% in the first 14 days. Pharmacokinetic sampling will be performed in approximately 12 patients.

Part 1:

Approximately 120 eligible patients will be enrolled and randomized in a 1:1 ratio to receive varlitinib and capecitabine (n=60) or placebo and capecitabine (n=60).

Part 2:

Approximately 350 eligible patients will be enrolled and randomized in a 1:1 ratio to receive varlitinib and capecitabine (n=175) or placebo and capecitabine (n=175).

In both Part 1 and Part 2 of the study, patients will be will be stratified by:

- region - US and the rest of world (ROW) and;
- primary tumor location - gallbladder vs non-gallbladder.

5.3.2 Inclusion Criteria

To be eligible for study entry patients must satisfy all of the following criteria:

1. Are of or older than the legal age in the respective countries at the time when written informed consent is obtained
2. Have histologically or cytologically confirmed advanced (unresectable) or metastatic biliary tract cancer, including intrahepatic or extrahepatic cholangiocarcinoma (CCA), gallbladder cancer, and carcinoma of Ampulla of Vater. This includes clinical diagnosis of biliary tract cancer with histological confirmation of adenocarcinoma.
3. Have received and failed one and only one prior line of systemic treatment for advanced or metastatic disease with radiologic evidence of disease progression. This prior line of systemic treatment must also contain gemcitabine.

4. Have received at least 6 doses of gemcitabine containing treatment in first line (Adjuvant therapy is not regarded as 1st line therapy)
5. Have radiographically measurable disease based on RECIST v1.1 as assessed by Independent Central Review (ICR) (For Part 1).
6. Have no evidence of biliary duct obstruction, unless obstruction is controlled by local treatment or, in whom the biliary tree can be decompressed by endoscopic or percutaneous stenting with subsequent reduction in bilirubin to below or equal to 1.5 × upper level of normal (ULN)
7. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
8. Are able to understand and willing to sign the informed consent form (ICF)
9. Have adequate organ and hematological function:
   a. Hematological function, as follows:
      - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
      - Platelet count $\geq 100 \times 10^9$/L
   b. Renal functions, as follows:
      - Estimated glomerular filtration rate or creatinine clearance > 50 mL/min/1.73m^2
   c. Hepatic function, as follows:
      - Albumin $\geq$ 3g/dL
      - Total bilirubin $\leq 1.5 \times$ ULN
      - ALT and AST $\leq 5 \times$ ULN

5.3.3 Exclusion Criteria

Patients will be excluded from the study if one or more of the following criterion is applicable:

1. Are currently on or have received anti-cancer therapy within the past 3 weeks before receiving the first dose of study medication
2. Are currently on or have received radiation or local treatment within the past 3 weeks for the target lesion(s) before receiving the first dose of study medication
3. Have evidence of multiple ($\geq$ 2) peritoneal metastases or ascites at baseline as assessed by ICR (For Part 1). (Ascites which can be attributed by non-malignant causes is not excluded. Minimal ascites, which does not require paracentesis is permitted.)
4. Have had major surgical procedures within 14 days prior to first dose of study medication
5. Have a known metastatic brain lesion(s), including asymptomatic and well controlled lesion(s)
6. Have malabsorption syndrome, diseases significantly affecting gastrointestinal function, resection of the stomach or small bowel, or difficulty in swallowing and retaining oral medications which in the opinion of the Investigator could jeopardize the validity of the study results
7. Have uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, unstable angina pectoris, cardiac arrhythmia, diabetes, hypertension, or psychiatric illness/social situations that would limit compliance with study requirements

8. Have any history of other malignancy unless in remission for more than 1 year (non-melanoma skin carcinoma and carcinoma-in-site of uterine cervix treated with curative intent is not exclusionary)
9. Are female patients who are pregnant or breast feeding
10. Have been previously treated with varlitinib or have been previously treated with capecitabine as first line therapy for advanced or metastatic disease. For patients who have previously received capecitabine as a radiosensitizer or as part of their adjuvant therapy and their disease has relapsed for more than 6 months after their last dose of capecitabine adjuvant therapy, their capecitabine therapy will not be considered as a line of systemic chemotherapy for metastatic/advanced disease and thus they can participate in the study
11. Have received any investigational drug (or have used an investigational device) within the last 14 days before receiving the first dose of study medication
12. Have unresolved or unstable serious toxicity (≥ common terminology criteria for adverse events [CTCAE] 4.03 Grade 2), with the exception of anemia, asthenia, and alopecia, from prior administration of another investigational drug and/or prior cancer treatment
13. Have a known positive test for human immunodeficiency virus, hepatitis C (treatment naïve or after treatment without sustained virologic response), or hepatitis B infection with hepatitis B virus deoxyribonucleic acid exceeding 2000 IU/mL
14. Have a known history of drug addiction within last 1 year which, in the opinion of the Investigator, could increase the risk of non-compliance to investigational product
15. Need continuous treatment with proton pump inhibitors during the study period
16. Have a history of (non-infectious) pneumonitis that required steroids or current pneumonitis, or have a history of interstitial lung disease or current interstitial lung disease
17. Have any history or presence of clinically significant cardiovascular, respiratory, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic or psychiatric disease or any other condition which in the opinion of the Investigator could jeopardize the safety of the patient or the validity of the study results
18. Have a baseline corrected QT interval (Fridericia's formula) (QTcF) > 450 ms or patients with known long QT syndrome; torsade de pointes; symptomatic ventricular tachycardia; an unstable cardiac syndrome in the past 3 months before screening visit; > class 2 New York Heart Association heart failure; or > class 2 angina pectoris; or receiving quinidine, procainamide, disopyramide, amiodarone, dronedarone, arsenic, dofetilide, sotalol, or methadone. Please also see prohibited medication/therapy (Section 5.4.10.1 _Prohibited_Medication/Therapy)

5.3.4 Removal of Patients from Therapy or Assessments

A patient may withdraw from the study for any reason without prejudice to further treatment. A patient can be withdrawn from the study for any of the following reasons:

- Patient voluntarily withdraws from participation*
- Radiographic disease progression*

- Clinical disease progression
- Unacceptable toxicity*
- Patient's withdrawal of consent*
- Death
- Pregnancy
- Significant protocol deviation
- Lost to follow-up*
- If deemed by the Investigator that it is not in patient's interest to continue in the study

** Further details provided below.*

Patients who do not comply with the protocol or who withdraw consent will be replaced in the Safety lead-in part only. Patients who stop study drug for any other reasons will not be replaced. Withdrawn patients will not be replaced in Part 1 and Part 2. The reason(s) for withdrawal will be documented in the case report form (CRF).

The sponsor also has the right to terminate the study at any time in case of serious adverse events (SAEs) or if special circumstances concerning the study medication or the company itself occur, making further treatment of patients impossible. In this event, the Investigators will be informed of the reason for study termination. All patients receiving active treatment and who, in the opinion of the investigator, may benefit from continued varlitinib treatment, will be offered participation in an open-label extension study where only varlitinib will be provided by the sponsor or be managed under a compassionate use program governed by the regulatory authorities in the respective countries.

Withdraws from participation (follow-up permitted): Patients withdrawing from the study treatment will be encouraged where possible to return to the site for a study follow-up visit, particularly for safety evaluations, tumor assessments, and survival follow-up. In Part 1 and Part 2 of the study, patients will be followed up for survival when they withdraw from the study treatment every 12 weeks after the end of treatment (EOT) visit until death or up to data cut-off (DCO) of the study, whichever occurs first.

In this instance, it is important to note that the patient is ceasing participation, NOT withdrawing consent.

Radiographic disease progression: Sites should continue to perform radiological assessments until disease progression (or death in the absence of progression) in accordance with RECIST v1.1. Patients will be withdrawn from the treatment if there is radiological evidence of disease progression as defined by RECIST v1.1. Additional radiological assessments of disease will not be undertaken unless there is a clinical indication (such as additional symptoms or signs). If radiological progression is equivocal, for example within the bounds of measurement error, it is recommended to continue randomized study treatment until the next scheduled assessment and reassess. Once permanently discontinued, randomized study medication cannot be re-started.

Unacceptable toxicity: If the symptoms are not controlled with standard treatments and are considered to be clinically significant, study therapy will be stopped and the patient

will be withdrawn from the study treatment. Refer to Section 5.4.8.1 for more details of dose interruption/resumption/modification. Patients removed from study treatment for unacceptable toxicity will be followed until resolution or stabilization of the AE. Patients who are withdrawn from treatment prior to radiographic disease progression should continue to be followed until progression in accordance with the study plan.

Consent Withdrawal: Patients may withdraw from the study at any time at their own request. The withdrawal of consent should be explained in detail in the medical records by the Investigator and entered on the appropriate CRF page. Details of withdrawal should indicate whether the withdrawal is from further treatment with study medication only or also from study procedures and/or post treatment study follow-up. Patients who request to withdraw from further treatment and study procedures may be followed up for OS (if consented by patients).

The Investigator should inquire about the reason for withdrawal and request that the patient return all unused study medication. The Investigator should also ask the patient to return for a final visit, if applicable, and follow-up with the patient regarding any unresolved AEs.

Lost to follow-up: If a patient does not return for a scheduled visit, every effort should be made at least once every month to contact the patient to reschedule the visit, including mandatory telephone contact and written letter; as well as on a case-by-case basis patient visit. All efforts should be documented in the patient's medical source record. Patient is considered lost to follow-up if patient cannot be reached after 3 months from the scheduled visit or before date of DCO, whichever is earlier.

All patients who are withdrawn or discontinued from the study are required to complete a safety follow-up visit within 28 days after the last administration of study medication, where possible. If the Investigator is unable to complete the safety follow-up visit assessments, the reason(s) must be recorded in the eCRF. All AEs/SAEs will be collected until 28 days after the last administration of study medication.

If a patient discontinues study treatment and is withdrawn from the study for any reason, the study center must immediately notify the medical monitor. The Investigator should also ensure the return of unused study medication.

5.3.5 Pregnancy

There is no information regarding the effects varlitinib could have on the development of a human fetus. Capecitabine may cause fetal harm if given to a pregnant woman. Capecitabine causes embryolethality and teratogenicity in mice and embryolethality in monkeys when administered during organogenesis[12]. Therefore, it is important that females and the partners of male patients do not become pregnant during the study and for at least 3 months after the patient has taken their last dose of varlitinib.

Female patients of child bearing potential and men enrolled in this study, in addition to partners of male patients must agree to use adequate contraception (as listed in Section 5.3.5.1) prior to study entry, for the duration of study participation, and for 3 months following completion of varlitinib/placebo or capecitabine therapy.

A female of child-bearing potential is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- Has not undergone a hysterectomy or bilateral oophorectomy; or
- Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

5.3.5.1 Acceptable Forms of Contraception

A highly effective method of birth control is defined as those which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly.
Individually hormonal, barrier or intrauterine device methods alone are not acceptable.
Examples of acceptable forms of highly effective contraception for women include:

- Established use of oral, injected or implanted hormonal methods of contraception in combination with a barrier method*
- Placement of an intrauterine device or intrauterine system in combination with a barrier method
- Sterilized male partner (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate) in combination with a barrier method
- True abstinence: When this is in line with your preferred and usual lifestyle

Examples of non-acceptable methods of contraception include:
- Barrier method alone
- Periodic abstinence (e.g., calendar, ovulation, sympthothermal, post ovulation)
- Withdrawal
- Spermicide

*Barrier methods include: diaphragm, cervical cap, and condom.

For men, it is recommended that a condom be worn for all sexual intercourse (in addition to another effective means of contraception) as it is not known if study drug may affect sperm risking the potential for congenital abnormalities.

5.3.5.2 Time Period for the Collection of Pregnancy Information

All pregnancies in female patients and in female partners of male patients receiving study drug will be recorded from enrolment until 3 months after last dose of varlitinib/placebo or capecitabine.

5.3.5.3 Follow-up in the Event of a Pregnancy

Should a woman become pregnant or suspect she is pregnant while participating in this study, or should a male patient's partner become pregnant or suspect she is pregnant while the male is participating in this study, the treating Investigator should be informed immediately. Female patients will be withdrawn from study treatment, and all pregnancies will be reported along the same timelines as a SAE.

If a female patient or the female partner of a male patient who has received study drug becomes pregnant the pregnancy will be recorded. The independent ethics committee (IEC) and the Sponsor will be informed. In all cases of pregnancy, the patient will be asked to provide information on the outcome of the pregnancy, including premature termination should the case arise.

Spontaneous miscarriage and congenital abnormalities will be reported as a SAE.

The follow-up period will be deemed to have ended when the health status of the child has been determined on its birth and followed up for eight weeks following the birth for any potential abnormalities.

5.4 Investigational Products

5.4.1 Study Medication Administered

In the Safety lead-in, eligible patients will receive varlitinib plus capecitabine (n=12 to 20).

In Part 1 and Part 2 of the study, eligible patients will be randomized into 2 arms; experimental arm will receive varlitinib plus capecitabine (part 1: n=60; part 2: n=175) or control arm will receive placebo plus capecitabine (part 1: n=60; part 2: n=175).

Study medications are presented in Table 3 and Table 4.

Table 3: Investigational Product

Investigational Products	Dose form	Route	Dose (mg)	Dose frequency	Duration*
Varlitinib	Tablet	Oral	300 mg	BID	Every day in a 21-day cycle
Placebo	Tablet	Oral	Not Applicable	BID	Every day in a 21-day cycle

Abbreviation: BID = twice daily.
*Treatment will continue until disease progression assessed by the Investigator as per RECIST version 1.1, unacceptable toxicity, withdrawal of consent, or death.

Table 4: Background Therapy

Background Therapy	Dose form	Route	Dose (mg)	Dose frequency	Duration*
Capecitabine	Tablet	Oral	1000 mg/m^2	BID	14 days (Day 1-14) followed by 7 days rest in a 21-day cycle

Abbreviation: BID = twice daily.
*Treatment will continue until disease progression assessed by the Investigator as per RECIST version 1.1, unacceptable toxicity, withdrawal of consent, or death.

5.4.2 Identity of Investigational Products and Background Therapy

Varlitinib

ASLAN will supply the varlitinib tablets.

Varlitinib tablets consist of varlitinib (ASLAN001) (as free base), lactose monohydrate, hydroxypropyl cellulose, croscarmellose sodium, magnesium stearate, and Opadry II yellow film-coat. The tablets are yellow, round, standard convex, film-coated tablets, 5/16 inch in diameter.

Placebo

ASLAN will supply the matching placebo tablets.

Placebo tablets will be identical in appearance to varlitinib tablets; yellow, round, standard convex, film-coated tablets, 5/16 inch in diameter.

Capecitabine

Capecitabine (XELODA®) will be sourced centrally and be supplied to the study by ASLAN for Safety lead-in Part 1 and Part 2. For the study lead-in and after the Part 1 DCO, capecitabine (does not have to be XELODA® if other commercial brands are more readily available at the site) can also be supplied by the study site, if needed.

Capecitabine is a fluoropyrimidine carbamate with antineoplastic activity. It is an orally administered systemic prodrug of 5'-deoxy-5-fluorouridine, which is converted to 5-fluorouracil.

Capecitabine is a white to off-white crystalline powder with an aqueous solubility of 26 mg/mL at 20ºC. Capecitabine is supplied as biconvex, oblong film-coated tablets for oral administration. Tablets are supplied as either 150 mg or 500 mg strength capecitabine.

The inactive ingredients in capecitabine include: anhydrous lactose, croscarmellose sodium, hydroxypropyl methylcellulose, microcrystalline cellulose, magnesium stearate and purified water. The peach or light peach film coating contains hydroxypropyl methylcellulose, talc, titanium dioxide, and synthetic yellow and red iron oxides.

Refer to the XELODA® (capecitabine) prescribing information leaflet for additional details[12].

5.4.3 Storage Condition of Study Medications

Varlitinib/Placebo

It is recommended that varlitinib/placebo is stored up to 25ºC (77 ºF) protected from light.

No special procedures for the safe handling of varlitinib are required.

Capecitabine

It is recommended that capecitabine is stored, as per the instruction on the package insert, at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F).

The storage area of the study center has to be a secure, temperature controlled, locked room with restricted access. Study centers will be required to keep a temperature log to establish a record of compliance with these storage conditions.

Accurate records must be kept regarding dispensing and return of study medication for each individual patient in the study. Reasons for inconsistency from the expected dispensing or return of study medication must be recorded. The Sponsor will be permitted upon request to audit the supplies, storage, dispensing procedures and records.

5.4.4 Packaging and Labeling

All packaging and labeling operations will be performed according to Good Manufacturing Practice for Medicinal Products and the relevant regulatory requirements.

Varlitinib, matching placebo and capecitabine tablets (Part 1 and 2 only*) are packaged in DosePak wallet with Child-Resistant ATSM Index class XIIIA re-closable semi rigid blister packaging.

*Since each site's pharmacy will be supplying their own capecitabine in the Safety lead-in part of the study and after the Part 1 DCO, the packaging and labeling will be dependent on their selected brand.

5.4.5 Method of Assigning Patients to Treatment Groups

Safety Lead-in:

The Safety Lead-in part of the study has a non-randomized single arm design. All eligible patients will receive varlitinib 300 mg BID, every day plus capecitabine 1000 mg/m^2 BID, Day 1 to 14, followed by a 7-day rest period (21-day cycle).

Each patient's eligibility will be reviewed by the medical monitor during the screening period. Patients will be sequentially enrolled after being screened for eligibility and providing consent.

At screening, potential patients will be assigned a unique screening number that starts with "S" and 4 digits (i.e., S1001) manually or by electronic data capture system.

In the case of discontinuation of chemotherapy due to toxic effects, varlitinib or placebo therapy will be continued until disease progression, the development of unacceptable toxicities, or withdrawal of consent or death.

After the DCO in Part 1, all patients receiving treatment including those from the Safety Lead-in and who, in the opinion of the investigator, may benefit from continued varlitinib treatment, will be offered participation in an open-label extension study where only varlitinib will be provided by the sponsor; or be managed under a compassionate use program governed by the regulatory authorities in the respective countries.

Parts 1 and 2:

At the initial screening visit, the Investigator or suitably trained delegate will:

1. Obtain signed ICF (main study) from the potential patient before any study specific procedures are performed.
2. Potential patients will be assigned a unique screening number that starts with "S" and 4 digits (i.e., S1001) by electronic data capture system. This screening number will be sequential from Safety lead-in, and will not be repeated.
3. Determine patient eligibility. See Section 5.3.2 and Section 5.3.3.
4. Once the patient is confirmed to be eligible, the Investigator or suitably trained delegate will assign eligible patient a unique randomization number via Randomization and Trial Supply Management (RTSM) system. Randomization numbers will start with "R" followed by 4 digits (i.e., R1001 for part 1, R2001 for part 2) and will be assigned strictly sequentially by RTMS (starting at R1001, R2001 in part 1 and 2, respectively), as patients are eligible for randomization. This number is the patient's unique identifier and is used to identify the patient with the assigned treatment. This randomization number will be available to the Investigator in the electronic data capture system.

5.4.6 Procedures for Randomization

Patients must not be randomized unless all eligibility criteria have been met. For Part 1 only, this includes receiving eligibility confirmation from the ICR.

Patients who satisfy all the entry criteria will be centrally assigned to study treatment by the RTSM, according to the randomization scheme generated by the designated CRO. Patients will be randomized in a 1:1 ratio to either varlitinib or placebo, both on a background of capecitabine (n=120 for Part 1 and n=350 for Part 2). The randomization scheme will be stratified by the following 2 covariates:

- Geographical region - US or ROW
- Primary tumor location – gallbladder (GB) or non-GB

The actual treatment given to patients will be determined by the randomization scheme in RTSM. The randomization scheme will be produced using SAS® version 9.4, which incorporates a standard procedure for generating randomization numbers. One randomization list will be produced containing sufficient random numbers for each of the 4 randomization strata. A blocked randomization will be generated and all centers will use the same list in order to minimize any imbalance in the number of patients assigned to each treatment group.

The dose and regimen of randomized therapy to be administered is as follows:

- Varlitinib 300 mg BID, every day
- Placebo BID, every day

Patients in both arms will receive background chemotherapy with capecitabine 1000 mg/m^2 BID, Day 1 to 14, followed by a 7-day rest period (21-day cycle).

Patients will be identified to the Centralized Randomization Center using site number, screening number, randomization number, gender, and date of birth. Patients will be randomized strictly sequentially within each stratum, as patients are eligible for randomization. The RTSM will inform the Investigator of the Kit ID number to be allocated to the patient at each dispensing visit via electronic data capture (EDC).

Study medication should only be dispensed to each randomized patient at the Cycle 1 Day 1 visit. It is allowed to randomize patient up to 24 hours prior to first dose. The first dose of study medication must only be administered in the morning of Cycle 1 Day 1 after pre-dose assessment (e.g., safety laboratory sampling, electrocardiogram [ECG], PK sampling) are completed. The day on which a patient takes the first dose of study medication will be considered Cycle 1 Day 1.

The Kit ID number dispensed at each visit will correspond to the treatment to which the patient was originally randomized.

If a patient discontinues participation in the study, then their screening/randomization number cannot be reused.

5.4.7 Selection of Doses in the Study

Varlitinib

The MTD of varlitinib in combination with capecitabine 1000 mg/m^2 BID was determined to be 400 mg BID in a previous study of the varlitinib/capecitabine combination therapy (Study ARRAY-543-204). Considering that patients with BTC who have failed one line of systemic therapy are usually frail with multiple co-morbidities, the dose of varlitinib selected for this study is 300 mg BID in combination with capecitabine. This dose combination of varlitinib and capecitabine will be assessed for safety and tolerability in the first 12 patients in the Safety lead-in, prior to randomization of patients in Parts 1 and 2 of the study.

Capecitabine

In this study capecitabine will be administered as 1000 mg/m^2 BID for 14 days followed by 1-week rest. Refer to Table 5 for the dose calculation. Capecitabine tablets are available in 2 dosage strengths, 500mg and 150mg. In order to allow improved patient compliance and to be in line with routine clinical practice, it is allowed for patient to be dosed with ± 5% deviation from the Dose per administration (mg) listed in Table 5 to reduce number of capecitabine tablets used.

The dosage, PK, and safety of capecitabine (1000 mg/m^2 BID, Day 1 to Day 14, followed by a 7-day rest period) have been established in the ARRAY-543-204 Phase I study. This dose of capecitabine has been successfully used with varlitinib in patients with advanced metastatic breast cancer (ASLAN001-003) and in a study (NCT00078572) conducted by Geyer, et al. where capecitabine was used in combination with lapatinib in metastatic breast cancer.[11] This dose of capecitabine is also supported by an article by Patt et al. 2004.[13]

Table 5: Dose Calculations for Starting Dose of Capecitabine of 1000 mg/m^2

Full dose 1000 mg/m^2	**Number of 150 mg tablets and/or 500 mg tablets per administration (each administration to be given morning and evening)**			**Reduced dose (75%) 750 mg/m^2**	**Reduced dose (50%) 500 mg/m^2**
Body Surface Area (m^2)	Dose per administration (mg)	150 mg	500 mg	Dose per administration (mg)	Dose per administration (mg)
≤1.26	1150	1	2	800	600
1.27 - 1.38	1300	2	2	1000	600
1.39 - 1.52	1450	3	2	1100	750
1.53 - 1.66	1600	4	2	1200	800
1.67 - 1.78	1750	5	2	1300	800
1.79 - 1.92	1800	2	3	1400	900
1.93 - 2.06	2000	-	4	1500	1000
2.07 - 2.18	2150	1	4	1600	1050
≥ 2.19	2300	2	4	1750	1100

5.4.8 Selection and Timing of Dose for Each Patient

Safety Lead-in

Varlitinib will be administered BID with a meal or within 30 minutes after food intake, approximately at the same time (±2 hours), in the morning and evening each day, using the appropriate number of 100 mg tablets. High fat meal should be avoided and varlitinib tablets should not be chewed, crushed, or broken.

On Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 1 Day 14, varlitinib tablets (morning dose) can only be administered under the supervision of the Investigator (or designee).

Capecitabine will be administered with food at the same time as varlitinib BID for 14 days with 7 days rest in a 21-day cycle.

A sample low fat meal is:

Food Item	Calories (kcal)	Fat (g)	Carbohydrate (g)	Protein (g)
2 slices of white bread toast	134	1.7	25	3.8
1 tablespoon light fat margarine*	59	6.6	Trace	Trace
1 tablespoon jelly	55	Trace	14	Trace
8 fluid ounces of skim milk	86	0.4	11.8	8.4
Total calories (kcal)	334	78	206	50
% of total calories	100	23	62	15

* Margarine spread: approximately 48% fat. Source: USDA National Nutrient Database for Standard reference, 2010

*Type of low fat meal to be given with varlitinib should be based on the investigator's judgement

During the Cycle 1 Day 1 and Day 8 visits, the morning meal will be a small snack to be taken approximately 30 minutes prior to morning dosing of varlitinib. Patients will remain fasted until after the 6-hour ECG/PK assessment when they will receive a snack/small meal. The next meal can be taken after the 8.5-hour ECG/PK assessment. Timing and type of meal will be recorded on the CRF.

Part 1 and 2

Varlitinib or placebo will be administered BID with a meal or within 30 minutes after food intake, approximately at the same time (±2 hours), in the morning and evening each day, using the appropriate number of 100 mg tablets. High fat meal should be avoided and varlitinib tablets should not be chewed, crushed or broken.

Retake of one dose of varlitinib or placebo is allowed if patient vomits within 30 minutes after administration of varlitinib or placebo. Retaking of varlitinib is not allowed if patient vomits again upon first retake.

On Cycle 1 Day 1 and Cycle 1 Day 8 (Part 1 only), Cycle 2 Day 1, varlitinib tablets (morning dose) can only be administered under the supervision of the Investigator (or designee).

Capecitabine will be administered with food at the same time as varlitinib or placebo BID for 14 days with 7 days rest in a 21-day cycle. Dose modification details are provided in Section 5.4.8.1.

Study medication will be dispensed to each patient to take at home after leaving the study center until the next scheduled visit. The study medication is to be taken until the patient

experiences an unacceptable toxicity, withdraws consent, disease progression (as assessed by the Investigator based on RECIST version 1.1 [Appendix 14.1]), or death.

5.4.8.1 Dose Modification

If a patient experiences a clinically significant adverse event of CTCAE 4.03 Grade 3 and above, not attributable to the disease or disease-related processes under investigation, dosing of investigational product and/or background therapy will be interrupted or the dose reduced and supportive therapy administered as required*. Any change in study medication needs to be recorded in the CRFs along with the reason for the change.

*Note: In the Safety lead-in, treatment will continue for a minimum of 14 days, during which time dose adjustment is not allowed. Dose adjustment and interruption is allowed from Day 15 onwards.

The recommended dose adjustment schedule for the investigational product (varlitinib/placebo) and capecitabine are described in Table 6 and Table 7 below, respectively, with the exception of hyperbilirubinemia, as well as serum creatinine increase, which are described separately in Section 5.4.8.2. Clinical judgment of the treating investigator should guide the management plan for each patient based on individual benefit/risk assessments.

Table 6: Recommended Dose Adjustments for Varlitinib/Placebo

Toxicity (NCI CTCAE 4.03 Grades)	During a Course of Therapy	Dose Adjustment for Next Treatment
Grade 1 and 2	Maintain dose level	Maintain dose level
Grade 3 and above		
1st appearance	Interrupt until resolved to grade 0-2	300 mg BID
2nd appearance		200 mg BID
3rd appearance		100 mg BID
4th appearance	Discontinue treatment permanently	-

Abbreviations: BID = twice daily, NCI CTCAE = The National Cancer Institute Common Terminology Criteria for Adverse Events.

Table 7: Recommended Dose Adjustment for Capecitabine

Toxicity (NCI CTCAE 4.03 Grades)	During a Course of Therapy	Dose Adjustment for Next Treatment
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
1st appearance	Interrupt until resolved to grade 0-1	1000 mg/m^2
2nd appearance		750 mg/m^2
3rd appearance		500 mg/m^2
4th appearance	Discontinue treatment permanently	-
Grade 3		
1st appearance	Interrupt until resolved to grade 0-1	750 mg/m^2
2nd appearance		500 mg/m^2
3rd appearance	Discontinue treatment permanently	-
Grade 4		
1st appearance	Discontinue permanently OR If physician deems it to be in the patient's best interest to continue, interrupt until resolved to Grade 0-1	500 mg/m^2

Abbreviation: NCI CTCAE = The National Cancer Institute Common Terminology Criteria for Adverse Events.

Any interruption in dose or reduction in dose of study medication and background therapy needs to be captured in the CRF. In the event that the administration of varlitinib/placebo or capecitabine is interrupted for longer than 6 consecutive weeks, varlitinib/placebo or capecitabine must be permanently withdrawn. If capecitabine is permanently withdrawn, patients are allowed to continue in the study on varlitinib/placebo until disease progression, unacceptable toxicity, withdrawal of consent, or death. Similarly, in the event that varlitinib/placebo is permanently withdrawn, patients are allowed to continue

in the study on capecitabine until disease progression, unacceptable toxicity, withdrawal of consent, or death.

5.4.8.2 Management of Toxicities

Management of Gastrointestinal Toxicities attributable to Varlitinib

Diarrhea:

For the management of diarrhea for patients in this study, routine loperamide prophylaxis as a standby is recommended. The recommend dose of loperamide is 2 mg three times a day (TID). Buscopan or a similar antispasmodic agent is recommended for management of acute symptoms. The recommended initial dose of Buscopan is 20 mg TID and can be escalated to 20 mg QID.

The pharmacologic interventions for treatment emergent diarrhea should include:

First line therapy – loperamide

- If receiving routine loperamide prophylaxis, increase dose to a maximum of 16 mg/day.
- If new-onset diarrhea, take loperamide 4 mg with first bout of diarrhea followed by 2 mg every 4 hours or after every unformed stool (maximum 16 mg/day). Continue until diarrhea-free for 12 hours.
- With recovery to $\leq$ Grade 1, take loperamide 2 mg TID.

As a second line therapy for the treatment of diarrhea refer to Table 8.

Table 8: Recommended Management of Diarrhea Attributable to Varlitinib

Toxicity (NCI CTCAE 4.03 Grades)	Treatment	Dose Adjustment
Grade 1	If persistent diarrhea on loperamide, add diphenoxylate hydrochloride plus atropine sulfate (Lomotil®) 2.5 mg every 6 to 8 hours	Maintain dose level
Grade 2	If persistent diarrhea on loperamide, add octreotide (short acting) 150 µg SC TID, or after the initial dose of short acting octreotide, if well tolerated, a single dose of octreotide LAR 20 mg intramuscularly	Maintain dose level
Grade 3 or Grade 4	after intensive loperamide therapy, titrate loperamide to keep diarrhea controlled (< 4 stools/day)	1st occurrence Maintain dose level
	Octreotide (100 to 150 µg SC BID or 25 to 50 µg/hour IV if dehydration is severe, with dose escalation up to 500 µg SC TID	2nd occurrence Reduce Varlitinib/placebo dose to 200 mg BID
	IV fluids as appropriate	3rd or more occurrence Reduce Varlitinib/placebo dose to 100 mg BID
	consider prophylactic antibiotics, especially if diarrhea is persistent beyond 24 hours or if there is a fever or Grade 3 /4 neutropenia	

Abbreviations: BID = twice daily, IV = intravenous, NCI CTCAE = The National Cancer Institute Common Terminology Criteria for Adverse Events, SC = subcutaneous, TID = 3 times a day.

Nausea/Vomiting:

Both varlitinib and capecitabine are considered to have low to minimal emetic risk. Routine prophylaxis for nausea/vomiting is not recommended. Anti-emetic medications can be used on an as-needed basis (PRN). If nausea/vomiting recur in later cycles of treatment, prophylactic medications can be used on the discretion of Investigator. Several anti-emetic drugs have QT prolongation effects and therefore are not allowed in the Safety lead-in part of this study, which will assess the QTc prolongation effect of study medications. The recommended management of nausea/vomiting is listed in Table 9.

*Metoclopramide, dolasetron, granisetron, and ondansetron are prohibited in the Safety lead-in (Cycle 1 Day 1 to Cycle 2 Day 1) and Part 1 (Cycle 1 Day 1 to Cycle 2 Day 1) of this study due to their QT prolonging effect. These medications can be used with caution in Part 2 of this study (Section 5.4.10). From Cycle 2 Day 2 in the Safety lead-in and Part 1 of this study and in the event that symptoms cannot be controlled by panolosetron or patients are intolerant to panolosetron, then investigators are allowed to prescribe metoclopramide, dolasetron, granisetron, and ondansetron without prior approval. However for tracking purpose, Sponsor must be informed if the above medications have been used.

Table 9: Recommended Management of Nausea/Vomiting attributable to Varlitinib

Study part	Breakthrough treatment for acute symptom control	Prophylaxis for recurrent nausea/vomiting (start 30 mins before study treatment)
Safety lead-in Part1 (Cycle 1 Day 1 to Cycle 2 Day 1)	Olanzapine 5-10 mg PO QD PRN or Prochlorperazine: 5-10 mg every 6 hours PRN (maximum 40 mg/day)	Prochlorperazine: 10 mg PO and then every 6 hours PRN (maximum 40 mg/day) or Palonsetron: 0.25 mg IV every 5 days
Part 1 (Cycle 2 Day 2 and afterward) and Part 2	Olanzapine 5-10 mg PO QD PRN or Prochlorperazine: 5-10 mg every 6 hours PRN (maximum 40mg/day) or Metoclopramide: 10-20 mg PO/IV every 4-6 hours PRN or Dexamethasone 12 mg PO/IV and QD PRN* or Haloperidol 0.5-2 mg PO/IV every 4-6 hours Or one of the following: Dolasetron: 100 mg PO QD PRN Granisetron: 1-2 mg (total dose) PO QD PRN or 1 mg PO BID PRN or 1 mg IV QD PRN or 3.1 mg/24 hours transdermal patch every 7 days Ondansetron: 16-24 mg PO QD PRN or 8-16 mg IV QD PRN	Metoclopramide: 10-20 mg PO and then every 6 h PRN or Prochlorperazine: 10 mg PO and then every 6 hours PRN (maximum 40 mg/day) or one of the following: Dolasetron: 100 mg PO QD PRN Granisetron: 1-2 mg PO QD PRN or 3.1 mg/24 hours transdermal patch every 7 days Ondansetron: 8-16 mg PO QD PRN Palonsetron: 0.25 mg IV every 5 days

Abbreviations: BID = twice daily, IV = intravenous, PO = per oral, PRN = as needed, QD = once daily.
Taken from NCCN Guidelines version 1.2017: Antiemesis.
*: moderate CYP3A4 inhibitor, use with caution.

Management of hyperbilirubinemia and serum creatinine attributable to Varlitinib

Hyperbilirubinemia

The dose adjustment schedule for investigational product (varlitinib/placebo) when hyperbilirubinemia occurs in combination with an increase in transaminases (ALT, AST) of CTCAE 4.03 Grade 2 and above is described in Table 10.

Table 10: Recommended Dose Adjustment for Management of Hyperbilirubinemia with Increased Transaminases

Toxicity (NCI CTCAE 4.03 Grades)	During a Course of Therapy	Dose Adjustment for Next Treatment
Grade 1	Maintain dose level	Maintain dose level
Grade 2 and 3		
1st appearance	Interrupt until resolved to grade 0-1	300 mg BID
2nd appearance		200 mg BID
3rd appearance		100 mg BID
4th appearance	Discontinue treatment permanently	-
Grade 4		
1st appearance	Interrupt until resolved to grade 0-1	200 mg BID
2nd appearance	Interrupt until resolved to grade 0-1	100 mg BID
3rd appearance	Discontinue treatment permanently	-

Abbreviations: BID = twice daily, NCI CTCAE = The National Cancer Institute Common Terminology Criteria for Adverse Events.

If hyperbilirubinemia is primarily due to an increase in indirect bilirubin (with indirect bilirubin > direct bilirubin and direct bilirubin ≤ 1.5 × ULN) with no increase in transaminases levels (ALT, AST) or an increase in transaminases of ≤ Grade 1, follow the dose adjustment schedule in Table 11.

Table 11: Recommended Dose Adjustment for Management of Hyperbilirubinemia due to Indirect Bilirubin

Toxicity (NCI CTCAE 4.03 Grades)	During a Course of Therapy	Dose Adjustment for Next Treatment
Grade 1 and 2	Maintain dose level	Maintain dose level
Grade 3 and above		
1st appearance	Interrupt until resolved to grade 0-2	300 mg BID
2nd appearance		200 mg BID
3rd appearance		100 mg BID
4th appearance	Discontinue treatment permanently	-

Abbreviations: BID = twice daily, NCI CTCAE = The National Cancer Institute Common Terminology Criteria for Adverse Events.

Increased Serum creatinine

Dose adjustment schedule for investigational product (varlitinib/placebo) as a result of increased serum creatinine levels is described in the Table 12.

Table 12: Recommended Dose Adjustment for Management of Increase Serum Creatinine

Toxicity (NCI CTCAE 4.03 Grades)	During a Course of Therapy	Dose Adjustment for Next Treatment
Grade 1	Maintain dose level	Maintain dose level
Grade 2 and 3		
1st appearance	Interrupt until resolved to grade 0-1	300 mg BID
2nd appearance		200 mg BID
3rd appearance		100 mg BID
4th appearance	Discontinue treatment permanently	-
Grade 4		
1st appearance	Interrupt until resolved to grade 0-1	200 mg BID
2nd appearance	Interrupt until resolved to grade 0-1	100 mg BID
3rd appearance	Discontinue treatment permanently	-

Abbreviations: BID = twice daily, NCI CTCAE = The National Cancer Institute Common Terminology Criteria for Adverse Events.

5.4.9 Blinding

Part 1 and Part 2 of the study is a double-blind study and thus the Investigator, site staff and patients are all blinded to treatment. No individual-patient information that can potentially un-blind the Investigator or patient will be reported until the end of the study. The presentation of the placebo will be identical in appearance to the study drug.

A communication plan will describe the procedure for un-blinding the study. The Investigator at the site will have access to the details of the double-blind treatment for each patient. Access to these details will be via RTSM.

Note!: The Investigator may only break the code **if knowledge of the study medication is necessary to provide optimal treatment to the patient in an emergency situation**. Whenever possible, the Investigator must consult with the sponsor before breaking the code. The unblinding procedure is described in RTSM User Guide.

Emergency unblinding will not preclude patient's data being included in the study analyses. The primary efficacy analyses are performed on an intention-to-treat basis (Section 8.3.2, Section 8.3.3), and unblinding will not result in a patient being excluded from any analysis sets. Similarly, safety will be assessed using the safety population (Section 8.3.1), which includes all patients who received at least one dose of study drug, regardless of any subsequent unblinding. However, a listing of all cases requiring unblinding will be provided, including details of the reason for unblinding.

Unblinding of all study treatment assignment will be performed at the time of data cut-off (DCO) of Part 1 and Part 2 of the study respectively before primary analysis.

The data cut-off for the primary analysis of Part 1 will be the later of 3 months after Last Patient In (LPI) or when 70% of the patients (84 patients) have experienced PFS events, while the data cut-off for Part 2 will be when 247 OS events have occurred.

After the treatment allocation is unblinded post DCO, all patients receiving active treatment and who, in the opinion of the investigator, may benefit from continued varlitinib treatment, will be offered participation in an open-label extension study where only varlitinib will be provided by the sponsor; or be managed under a compassionate use program governed by the regulatory authorities in the respective countries.

5.4.10 Prior and Concomitant Therapy

Concomitant medication may be given as medically indicated. All patients will be asked to provide a complete list of concomitant medication including prescription, over-the-counter, complementary, and alternative medications that have been taken within 4 weeks before the first treatment visit. They must also inform the Investigator about any new medication started while on the study.

Details (including indication, doses, frequency, and start/stop dates) of concomitant medication taken, as well as concomitant therapy (including indication, start and stop dates) administered within 4 weeks before the first treatment visit, during the study , until the completion of the safety follow-up visit, must be documented in the medical record and the appropriate CRF.

Varlitinib

Varlitinib may cause a drug-drug interaction with other medications that are cytochrome P450 (CYP) 3A4, CYP2C8, CYP2C9 or CYP2C19 inducers, inhibitors, or substrates. Human CYP3A4 is the major route of metabolism of varlitinib, whereas CYP2C8 and CYP2C19 are minor routes. Due to the potential for drug interactions based on in vitro screens, concomitant use of moderate CYP3A4, CYP2C8, CYP2C9, and P-gp inducers or inhibitors will be recorded during the entire clinical study. Refer to the FDA's Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers.[14]

Examples of CYP2C8 substrates are:

- amodiaquine (antimalarial, anti-inflammatory)
- serivastatin (statin)
- paclitaxel (chemotherapeutic)
- repaglinide (antidiabetic)
- torasemide (loop diuretic)
- sorafenib (tyrosine kinase inhibitor)
- rosiglitazone (antidiabetic) - converted to active metabolites

Examples of strong CYP2C8 inhibitors (one that causes a > 5-fold increase in the plasma area under the plasma concentration-time curve (AUC) values or more than 80% decrease in clearance) are:

- gemfibrozil (hypolipidemic)

Examples of moderate CYP2C8 inhibitors (one that causes a > 2-fold increase in the plasma AUC values or 50% to 80% decrease in clearance):

- trimethoprim (antibiotic)

Examples of CYP2C8 inhibitors with unspecified potency:

- thiazolidinediones (antidiabetic)
- montelukast (leukotriene receptor antagonist)
- quercetin (anti-inflammatory) Examples of CYP2C8 inducer:
- rifampicin (antibiotic)

Varlitinib is a weak inhibitor of CYP2C8 and CYP2C9 with an IC50 of 3.2 μM and 10.6 μM, respectively. Its plasma protein binding is higher than 99% so the free fraction of varlitinib in the blood is not likely to reach that concentration.

In the Safety Lead-in and Part 1 of the study, non-excluded drugs that are associated with torsade de pointes and QTc prolongation (Appendix 14.4) or QT Prolongation without torsade de pointes (_Drugs_that_ProlongAppendix 14.5) should be at steady-state dosing for at least 2 weeks before enrollment. During the study, from 2 weeks before the first dose to up to and including Cycle 2 Day 1, the dose of such drugs should not be increased, and new drugs in either group should not be initiated without approval from medical monitor.

In addition to the above, in the Safety lead-in and Part 1 of the study, from Cycle 2 Day 2 onwards, the dose of drugs associated with torsade de pointes and QTc prolongation (Appendix 14.4) or QT prolongation without torsade de pointes (Appendix 14.5) ideally should not be increased. Every attempt should be made to minimize the initiation of such drugs (Appendix 14.4 or Appendix 14.5). The initiation of any such drugs (Appendix 14.4 or Appendix 14.5) requires the medical monitor's approval.

Capecitabine

Refer also to the XELODA® (capecitabine) prescribing information leaflet[12] for details of drug interactions with capecitabine.

5.4.10.1 Prohibited Medication/Therapy

Prohibited medications during this study will include

- any other antitumor treatment
- proton pump inhibitors
- warfarin
- strong CYP3A4 inhibitors
- any other investigational product
- herbal preparations
- H2 blocker can be given 3 hours after each dose of varlitinib.

Please see Appendix 14.3 _Prohibited_Concomitant_Medication/Tfor the list of prohibited medication/therapy.

5.4.11 Treatment Compliance

The administration of all study medications should be recorded in the appropriate sections of the CRF. Patients shall report any self-administered medication.

Patients will be issued with a diary card, which is to be returned to the study center at the next visit. Treatment compliance of self-administered study medication will be assessed by regular tablet counts on the patient diary card and the information will be recorded in the appropriate section of the CRF.

In the event of a study related procedure or an intolerable AE or AE ≥ CTCAE 4.03 Grade 3 (Section 5.4.8.1), patients may be counseled to interrupt dosing permanently or temporarily. Doses not taken in such instances do not count as planned dose administrations and do not constitute lack of compliance.

Patients must bring all containers of study medication and any remaining tablets as well as the patient diary card with them at each scheduled visit. Patients will be instructed to notify the study center personnel of missed doses. Dates of missed or held doses will be recorded on the CRF.

At each visit, patients will be issued a patient diary card, which contains clear instructions on how and when to take the study medication and to record the time and date of each dose.

Each patient will record on the patient diary card the number of tablets of study medication taken and the time of taking them daily. This diary card will be returned to the study center at each scheduled visit.

The recorded information is required to be entered into the eCRF by study center personnel.

6 TIMING OF STUDY PROCEDURES

Patients will provide written informed consent before any study-related procedures are performed.

The timing and details of study assessments for the Safety lead-in are provided in Table 1 and for Part 1 and Part 2 in Table 2.

6.1 Study Visits – Safety Lead-in

6.1.1 Screening Visit – Safety Lead-in

Screening will be performed up to 14 days prior to the first administration of the study medication and background medication (Cycle 1 Day 1). Prior to any evaluations being performed, written informed consent must be obtained and a screening number assigned. Patients will then be assessed for compliance with the inclusion and exclusion criteria. The following assessments will be performed:

- Demographic information
- Medical history, concomitant medication(s) and prior treatment(s)
- Physical examination and weight
- Vital signs
- Triplicate central 12-lead ECG
- ECOG performance status
- Collection of AEs
- Blood collected for hematology, clinical chemistry, coagulation, and serology
- Urine collected for urinalysis
- Blood collected for pregnancy test for female patients of childbearing potential
- CT/MRI of the chest, abdomen, and pelvis. Brain and/or bone lesions may be scanned, if applicable.

Any of these investigations may be repeated to allow patients to qualify for the study. If appropriate, and with prior approval from the sponsor or their designee, patients who fail screening or who pass screening but have not been treated may be re-screened. Where investigations are repeated, the most recent investigations should meet all inclusion and exclusion criteria.

6.1.2 Treatment Visits – Safety Lead-in

Cycle 1 Day 1, Day 8 and Day 14

Refer to Table 1 for assessment details and timing of the following assessments:

- Physical examination and weight
- Vital signs
- ECOG performance status
- Collection of AEs
- Concomitant medication review
- Blood collected for hematology and clinical chemistry
- Urine collected for urinalysis
- Pre-dose triplicate central 12-lead ECG at 45 minutes pre-dose and 5 minutes pre-dose on Cycle 1 Day 1 and Cycle 1 Day 8 only (NOTE: not required on Day 14)
- Pre-dose blood collected for PK analysis at 5 minutes pre-dose on Cycle 1 Day 1, 20 minutes pre-dose on Cycle 1 Day 8 and 5 minutes pre-dose on Cycle 1 Day 14
- Varlitinib administration
- Capecitabine administration
- Post-dose triplicate central 12-lead ECG at 1, 2, 3, 4, 5, 6, 8.5, and 12 hours post-dose (NOTE: not required on Day 14)
- Post-dose blood collected for PK analysis at 0.5, 1, 2, 3, 4, 5, 6, 8.5, 10, and 12 hours post-dose

When ECGs and PK samples are collected at the same time point, the PK samples are always collected after the ECGs.

Subsequent Cycles – Cycle 2 Day 1, Cycle 3 Day 1, etc. (±5 days)

Refer to Table 1 for assessment details and timing of the following assessments:

- Physical examination and weight
- Vital signs
- ECOG performance status
- Collection of AEs
- Concomitant medication review
- Blood collected for hematology and clinical chemistry
- Urine collected for urinalysis
- Varlitinib administration
- Capecitabine administration
- Triplicate central 12-lead ECG (3 hours post-dose)
- CT/MRI of the chest, abdomen, and pelvis. Brain and/or bone lesions may be scanned, if applicable every 6 weeks from Cycle 1 Day 1.

6.1.3 End of Treatment Visit (+ 7 Days) – Safety Lead-in

- Physical examination and weight
- Vital signs
- ECOG performance status
- Collection of AEs
- Concomitant medication review
- Urine or blood collected for pregnancy test for female patients of childbearing potential
- Blood collected for hematology, clinical chemistry, and coagulation
- Urine collected for urinalysis

EOT assessments should be performed before the start of new anti-tumor treatment.

6.1.4 Safety Follow up Visit 28 Days Post Last Study Medication Administration (+ 7 Days) – Safety Lead-in

- Physical examination and weight
- Vital signs
- Triplicate central 12-lead ECG
- ECOG performance status
- Collection of AEs
- Concomitant medication review
- Blood collected for hematology and clinical chemistry

If the patient needs to start a new anti-tumor treatment within 28 days post last study medication administration, the safety follow-up assessments should be performed within 1 day before the start of the new anti-tumor treatment.

6.2 Study Visits – Part 1

6.2.1 Screening Visit – Part 1

Screening will be performed up to 14 days prior to randomization (Cycle 1 Day 1). It may be extended up to 21 days subjected to a case by case review and approval by the Sponsor. Prior to any evaluations being performed, written informed consent must be obtained and screening number assigned.

Patients will then be assessed for compliance with the inclusion and exclusion criteria.

The following assessments will be performed:

- Demographic information
- Medical history, concomitant medication(s), and prior treatment(s)
- Physical examination and weight
- Vital signs
- Triplicate central 12-lead ECG
- ECOG performance status
- Collection of AEs
- Blood collected for hematology, clinical chemistry, coagulation, serology, cancer antigen 19.9 (CA19.9), and CEA
- Urine collected for urinalysis
- Blood collected for pregnancy test for female patients of childbearing potential
- Blood collected for retrospective analysis of biomarkers
- Information on acquired tumor mutations if available as part of medical history or during study participation
- Archival paraffin-embedded tumor tissues collected for future analysis (the minimum archival tumor tissue to be collected is 19 unstained slides of 5 microns)
- Biopsy for those patients who do not have enough archival tumor tissue (additional consent to be provided)
- CT/MRI of the chest, abdomen, and pelvis images must be performed within 21 days prior to Cycle 1 Day 1, brain and/or bone lesions may be scanned, if applicable.

6.2.2 Treatment Visits – Part 1

Cycle 1 Day 1

Refer to Table 2 for assessment details and timing of the following assessments:

- Physical examination and weight

- Vital signs
- ECOG performance status
- Collection of AEs
- Concomitant medication review
- Blood collected for hematology and clinical chemistry
- Urine collected for urinalysis
- Pre-dose triplicate central 12-lead ECG at 45 minutes pre-dose and 5 minutes pre-dose
- Pre-dose blood collected for PK analysis at 5 minutes pre-dose
- Varlitinib or placebo administration
- Capecitabine administration
- Post-dose triplicate central 12-lead ECG at 1.5, 3, 5, and 8 hours post-dose
- Post-dose blood collected for PK analysis at 1.5, 3, 5, and 8 hours post-dose

When ECGs and PK samples are collected at the same time point, the PK samples are always collected after the ECGs.

Cycle 1 Day 8 (±1 day)

Refer to Table 2 for assessment details and timing of the following assessments:

- Physical examination and weight
- Vital signs
- ECOG performance status
- Collection of AEs
- Concomitant medication review
- Blood collected for hematology and clinical chemistry including weekly liver function tests
- Urine collected for urinalysis
- Pre-dose triplicate central 12-lead ECG at 45 minutes pre-dose and 5 minutes pre-dose
- Pre-dose blood collected for PK analysis at 20 minutes pre-dose
- Varlitinib or placebo administration
- Capecitabine administration
- Post-dose triplicate central 12-lead ECG at 1.5, 3, 5, and 8 hours post-dose
- Post-dose blood collected for PK analysis at 1.5, 3, 5, and 8 hours post-dose

When ECGs and PK samples are collected at the same time point, the PK samples are always collected after the ECGs.

Cycle 1 Day 15 (±1 day)

Refer to Table 2 for assessment details and timing of the following assessment:

- Blood collected for weekly liver function tests
- Varlitinib or placebo administration

Cycle 2 Day 1 (±5 days)

Refer to Table 2 for assessment details and timing of the following assessments:

- Physical examination and weight
- Vital signs
- ECOG performance status
- Collection of AEs
- Concomitant medication review
- Blood collected for hematology and clinical chemistry
- Urine collected for urinalysis
- Varlitinib or placebo administration
- Capecitabine administration
- Post-dose triplicate central 12-lead ECG at 3 hours post-dose

Cycle 3 Day 1 (±5 days)

Refer to Table 2 for assessment details and timing of the following assessments:

- Physical examination and weight
- Vital signs
- ECOG performance status
- Collection of AEs
- Concomitant medication review
- Blood collected for hematology and clinical chemistry
- Urine collected for urinalysis
- Varlitinib or placebo administration
- Capecitabine administration
- Blood collected for retrospective analysis of biomarkers
- Blood collected for CA19.9 and CEA
- CT/MRI of the chest, abdomen, and pelvis. Brain and/or bone lesions as applicable

Subsequent Cycles from Cycle 4 Day1, Cycle 5 Day 1, etc. (±5 days)

Refer to Table 2 for assessment details and timing of the following assessments:

- Physical examination and weight
- Vital signs
- ECOG performance status
- Collection of AEs
- Concomitant medication review
- Blood collected for hematology and clinical chemistry

- Urine collected for urinalysis
- Varlitinib or placebo administration
- Capecitabine administration
- Blood collected for CA19.9 and CEA every 6 weeks from Cycle 1 Day 1
- CT/MRI of the chest, abdomen, and pelvis. Brain and/or bone lesions as applicable every 6 weeks from Cycle 1 Day 1
- Post-dose triplicate central 12-lead ECG at 3 hours post-dose every 2 cycles from Cycle 4 Day 1

End of Treatment Visit (+ 7 days) – Part 1

- Physical examination and weight
- Vital signs
- ECOG performance status
- Collection of AEs
- Concomitant medication review
- Urine or blood collected for pregnancy test for female patients of childbearing potential
- Urine collected for urinalysis
- Blood collected for hematology, clinical chemistry and coagulation
- Blood collected for CA19.9 and CEA. If the reason for EOT is due to radiological disease progressions and CA19.9/CEA have already been assessed with the most recent scans, then CA19.9/CEA at EOT can be omitted.

EOT assessments should be performed before the start of new anti-tumor treatment.

6.2.3 Safety Follow-up Visit 28 Days Post Last Study Medication Administration (+ 7 Days) – Part 1

- Physical examination and weight
- Vital signs
- Triplicate central 12-lead ECG 3 hours after light snack
- Blood collected for PK analysis within 25 minutes after ECG evaluation
- ECOG performance status
- Collection of AEs
- Concomitant medication review

If the patient needs to start a new anti-tumor treatment within 28 days post last study medication administration, the safety follow-up assessments should be performed within 1 day before the start of the new anti-tumor treatment.

6.2.4 Disease Status Follow-up Visit Every 6 Weeks (± 5 Days) Post End of Treatment until Disease Progression – Part 1

- Physical examination and weight
- Vital signs
- ECOG performance status

- CT/MRI of the chest, abdomen, and pelvis. Brain and/or bone lesions as applicable

6.2.5 Survival Follow-up Visit, Every 12 Weeks (± 7 Days) Post Disease Progression – Part 1

- Survival status contact
- Details of anti-cancer treatment

Note: Survival calls may be made in the week following the date of DCOs for the analyses, and if subjects are confirmed to be alive or if the death date is after the DCOs, these subjects will be censored at the date of the DCOs.

6.3 Study Visits – Part 2

6.3.1 Screening Visit – Part 2

Screening will be performed up to 14 days prior to randomization (Cycle 1 Day 1). It may be extended up to 21 days subjected to a case by case review and approval by the Sponsor. Prior to any evaluations being performed, written informed consent must be obtained and screening number assigned.

Patients will then be assessed for compliance with the inclusion and exclusion criteria.

The following assessments will be performed:

- Demographic information
- Medical history, concomitant medication(s), and prior treatment(s)
- Physical examination and weight
- Vital signs
- Triplicate central 12-lead ECG
- ECOG performance status
- Collection of AEs
- Blood collected for hematology, clinical chemistry, coagulation, serology, cancer antigen 19.9 (CA19.9), and CEA
- Urine collected for urinalysis
- Blood collected for pregnancy test for female patients of childbearing potential
- Blood collected for retrospective analysis of biomarkers
- Information on acquired tumor mutations if available as part of medical history or during study participation
- Archival paraffin-embedded tumor tissues collected for future analysis (the minimum archival tumor tissue to be collected is 19 unstained slides of 5 microns)
- Biopsy for those patients who do not have enough archival tumor tissue (additional consent to be provided)
- CT/MRI of the chest, abdomen, and pelvis images must be performed within 21 days prior to Cycle 1 Day 1, brain and/or bone lesions may be scanned, if applicable.

6.3.2 Treatment Visits – Part 2

Cycle 1 Day 1

Refer to Table 2 for assessment details and timing of the following assessments:

- Physical examination and weight
- Vital signs
- ECOG performance status
- Collection of AEs
- Concomitant medication review
- Blood collected for hematology and clinical chemistry
- Urine collected for urinalysis
- Pre-dose triplicate central 12-lead ECG (before a snack)
- Pre-dose blood collected for PK analysis at 5 minutes pre-dose
- Varlitinib or placebo administration
- Capecitabine administration
- Post-dose blood collected for PK analysis at 1-3 hours post dose, 3-5 hours post dose, and 5-8 hours post dose (Sparse PK sampling)

Cycle 1 Day 8 (±1 day)

Refer to Table 2 for assessment details and timing of the following assessment:

- Blood collected for weekly liver function tests
- Varlitinib or placebo administration
- Capecitabine administration

Cycle 1 Day 15 (±1 day)

Refer to Table 2 for assessment details and timing of the following assessment:

- Blood collected for weekly liver function tests
- Varlitinib or placebo administration

Cycle 2 Day 1 (±5 days)

Refer to Table 2 for assessment details and timing of the following assessments:

- Physical examination and weight
- Vital signs
- ECOG performance status
- Collection of AEs

- Concomitant medication review
- Blood collected for hematology and clinical chemistry
- Urine collected for urinalysis
- Pre-dose blood collected for PK analysis at 20 minutes pre-dose
- Varlitinib or placebo administration
- Capecitabine administration
- Post-dose triplicate central 12-lead ECG at 3 hours post-dose
- Post-dose blood collected for PK analysis at 1-3 hours post dose, 3-5 hours post dose, and 5-8 hours post dose (Sparse PK sampling)

Cycle 3 Day 1 (±5 days)

Refer to Table 2 for assessment details and timing of the following assessments:

- Physical examination and weight
- Vital signs
- ECOG performance status
- Collection of AEs
- Concomitant medication review
- Blood collected for hematology and clinical chemistry
- Urine collected for urinalysis
- Varlitinib or placebo administration
- Capecitabine administration
- Blood collected for retrospective analysis of biomarkers
- Blood collected for CA19.9 and CEA
- CT/MRI of the chest, abdomen, and pelvis. Brain and/or bone lesions as applicable

Subsequent Cycles from Cycle 4 Day 1, Cycle 5 Day 1, etc. (±5 days)

Refer to Table 2 for assessment details and timing of the following assessments:

- Physical examination and weight
- Vital signs
- ECOG performance status
- Collection of AEs
- Concomitant medication review
- Blood collected for hematology and clinical chemistry
- Urine collected for urinalysis
- Varlitinib or placebo administration
- Capecitabine administration
- Blood collected for CA19.9 and CEA every 6 weeks from Cycle 1 Day 1
- CT/MRI of the chest, abdomen, and pelvis. Brain and/or bone lesions as applicable every 6 weeks from Cycle 1 Day 1

- Post-dose triplicate central 12-lead ECG at 3 hours post dose every 2 cycles from Cycle 4 Day 1

End of Treatment Visit (+ 7 days) – Part 2

- Physical examination and weight
- Vital signs
- ECOG performance status
- Collection of AEs
- Concomitant medication review
- Urine or blood collected for pregnancy test for female patients of childbearing potential
- Urine collected for urinalysis
- Blood collected for hematology, clinical chemistry and coagulation
- Blood collected for CA19.9 and CEA. If the reason for EOT is due to radiological disease progressions and CA19.9/CEA have already been assessed with the most recent scans, then CA19.9/CEA at EOT can be omitted.

EOT assessments should be performed before the start of new anti-tumor treatment.

6.3.3 Safety Follow-up Visit 28 Days Post Last Study Medication Administration (+ 7 Days) – Part 2

- Physical examination and weight
- Vital signs
- ECOG performance status
- Collection of AEs
- Concomitant medication review

If the patient needs to start a new anti-tumor treatment within 28 days post last study medication administration, the safety follow-up assessments should be performed within 1 day before the start of the new anti-tumor treatment.

6.3.4 Disease Status Follow-up Visit Every 6 Weeks (± 5 Days) Post End of Treatment until Disease Progression – Part 2

- Physical examination and weight
- Vital signs
- ECOG performance status
- CT/MRI of the chest, abdomen, and pelvis. Brain and/or bone lesions as applicable

6.3.5 Survival Follow-up Visit, Every 12 Weeks (± 7 Days) Post Disease Progression – Part 2

- Survival status contact
- Details of anti-cancer treatment

6.4 Duration of Treatment

The duration of each patient's study involvement will be as follows:

Screening Period: Up to 14 days. It may be extended up to 21 days subjected to a case by case review and approval by the Sponsor.

Treatment Period:

- **Safety lead-in**: Study treatment will be given in 21-day cycles. Patients will receive investigational product and background medication until disease progression, development of unacceptable toxicity, withdrawal of consent or death. Patients will be followed for disease status every 6 weeks.
- **Part 1 and Part 2**: Study treatment will be given in 21-day cycles. Patients will receive investigational product and background medication until disease progression, development of unacceptable toxicity, withdrawal of consent or death. Patients will be followed for disease status every 6 weeks. After disease progression, all patients will be followed for survival every 12 weeks until death or until the DCO for Part 2 OS analysis.

Safety Follow-Up Period: Patients will complete a safety follow-up visit 28 days after the last dose of investigational product. If the patient needs to start a new anti-tumor treatment within 28 days post last study medication administration, the safety follow-up assessments should be performed within 1 day before the start of the new anti-tumor treatment.

Only in Part 1 and 2:

Follow-up Period: If patients have not experienced radiological progression at the time of treatment discontinuation, radiological assessments should continue every 6 weeks (± 5 days) until disease progression (Disease Status Follow-Up). After disease progression, all patients will be followed for survival every 12 weeks until death or until the DCO for the final OS analysis (Survival Follow-Up)

7 SAFETY, EFFICACY, PHARMACOKINETIC AND BIOMARKER VARIABLES

The planned schedule of assessments is presented in Section 6, Table 1 (Safety lead-in) and Table 2 (Part 1 and Part 2).

7.1 Safety, Efficacy Pharmacokinetic and Pharmacodynamic Measurements Assessed

7.1.1 Safety Assessments

7.1.1.1 Adverse Events

Adverse Event Definition

An AE is defined as any untoward medical occurrence in a clinical study patient administered a medicinal product which 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 a medicinal (investigational) product, whether or not it is related to the medicinal (investigational) 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 CRF under specific efficacy assessments. Fluctuations of pre-existing conditions that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

Surgical procedures planned before enrollment of the patient in the study are not considered AEs if the condition(s) was known before study inclusion. In the latter case, the medical condition should be reported in the patient's medical history.

Progression of the cancer of target disease under study is generally not considered an AE.

It is the responsibility of the Investigator to document all AEs that occur during the study. AEs will be elicited by asking the patient a non-leading question; for example, "Have you experienced any new or changed symptoms since we last asked/since your last visit?" Adverse events should be reported on the appropriate page of the CRF.

Serious Adverse Event Definition

An SAE is any untoward medical occurrence or effect that, at any dose,

- Results in death.
- Is life-threatening (an AE is life-threatening if the patient was at immediate risk of death from the event as it occurred, i.e., it does not include a reaction that might have caused death if it had occurred in a more serious form).
- Requires or prolongs inpatient hospitalization. (Complications occurring during hospitalization are AEs and are SAEs if they cause prolongation of the current hospitalization.)
- Results in persistent or significant disability/incapacity. (An AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the patient's ability to carry out normal life functions).
- Results in a congenital anomaly/birth defect.

In addition, medical and scientific judgement is required to decide if prompt notification is required in situations other than those defined for SAEs above. This may include any event that the Investigator regards as serious that did not strictly meet the criteria above but may have jeopardized the patient or required intervention to prevent one of the outcomes listed above, or that would suggest any significant hazard, contraindication, side effect, or precaution that may be associated with the use of the study medication.

Events related to disease progression will not be reported as SAEs unless the events lead to death, and the death will be reported as an SAE.

Hospitalization due to the following reasons does not need to be reported as an SAE:

- Reasons described in the protocol (i.e., drug administration, protocol required procedures);
- Surgery or procedure planned prior to entry into the study;
- Surgery or procedure planned for pre-existing conditions that do not worsen after entry into the study;
- Social/administrative reasons (i.e., due to distance between home and hospital, hospice placement for terminal care due to progressive disease, etc.).

Assessment of Severity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study using the CTCAE 4.03 criteria. The assessments will be based on the Investigator's clinical judgment. The severity of each AE and SAE recorded in the CRF should be assigned to one of the categories:

Grade 1:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2:	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living
Grade 3:	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
Grade 4:	Life-threatening consequences; urgent intervention indicated
Grade 5:	Death related to AE

All changes in severity must be recorded in the eCRF.

Assessment of Causality

Every effort will be made by the Investigator to assess the relationship of the AE, if any, to the investigational product (varlitinib/placebo) and the background therapy

(capecitabine). For both investigational product and background therapy, causality should be assessed using the categories presented as follows:

Definitely Related: A clinical event, including clinical laboratory test abnormality, occurring in a plausible time relationship to the medication administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug should be clinically plausible.

Probably Related: A clinical event, including clinical laboratory test abnormality, with a reasonable time sequence to the medication administration, unlikely to be attributes to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal.

Possibly Related: A clinical event, including clinical laboratory test abnormality, with a reasonable time sequence to the medication administration, but which could also be explained by concurrent disease or other drugs or chemicals. Information on the drug withdrawal may be lacking or unclear.

Unlikely Related: A clinical event, including clinical laboratory test abnormality, with little or no temporal relationship to medication administration, and which other drugs, chemicals or underlying disease provide plausible explanations.

Not Related: A clinical event, including clinical laboratory test abnormality that has no temporal relationship to the medication or has more likely alternative etiology.

NOTE: AEs listed as 'possibly, probably or definitely' related to the investigational product are considered to have a suspected 'reasonable causal relationship' to the investigational product. Adverse events listed as 'unlikely or unrelated" are considered have a suspected "unrelated" causal relationship to the investigational agent/intervention.

Action Taken

The Investigator will describe the action taken in the appropriate section of the CRF, as follows:

- None
- Varlitinib/placebo permanently withdrawn
- Capecitabine permanently withdrawn
- Varlitinib/placebo temporarily interrupted
- Capecitabine temporarily interrupted
- Varlitinib/placebo dose modified
- Capecitabine dose modified
- Concomitant medication/therapy
- Other, specify.

Follow-up of Adverse Events

All Investigators should follow up patients with AEs until the event is resolved, the patient is lost to follow-up or until, in the opinion of the Investigator, the event is stabilized or determined to be chronic. Details of AE resolution must be documented in the CRF.

Documentation and Reporting of Adverse Events

Adverse events will be recorded and reported from the patient's signing of the informed consent to the safety follow-up assessment. Prior to receiving study medication, only AEs that were assessed as related to study procedures will be recorded and reported.

If a patient begins a new anti-tumor therapy within 28 days after the last administration of study medication, the AE reporting period for non-serious AEs ends at the time the new therapy is started.

All AEs per the definition stated in the protocol that are observed, elicited by the Investigator or reported by the patient, regardless of their causal relation to study medication will be documented in source documents, captured in CRF and will be evaluated by the Investigator. All new AEs, as well as those that worsen in intensity or frequency relative to baseline, which occur during the defined AE collection period must be recorded.

Each AE should be described in detail: A medical diagnosis of the event (if a medical diagnosis cannot be determined, a description of each sign or symptom characterizing the event should be recorded), onset date, resolution date, a determination of whether the event is serious or not, severity, relationship to the study medication, action taken and outcome.

The minimum information required for each AE includes the following:

- Type of event
- Duration (start and end dates)
- Severity
- Changes in severity
- Seriousness
- Causality in relation to varlitinib/placebo
- Causality in relation to capecitabine
- Action taken in relation to varlitinib/placebo
- Action taken in relation to capecitabine
- Treatments in relation to event
- Outcome

Outcome

The Investigators are to record the 'Outcome to Date' using the following categories:

Fatal	The termination of life as a result of an AE
Not Resolved	One of the possible results of an AE outcome that indicates that the event has not improved or the patient has not recuperated
Resolved	One of the possible results of an AE outcome that indicates that the event has improved or the patient has recuperated
Resolved with Sequelae	One of the possible results of an AE outcome where the patient recuperated but retained pathological/clinical conditions resulting from the prior disease or injury (AE)
Unknown	Not known, not observed, not recorded, or refused

7.1.1.2 Reporting of Serious Adverse Events

Collection of SAEs starts from signing of ICF until 28 days after the last administration of study medication. Prior to receiving investigational product, only SAEs that were assessed as related to study procedures will be reported.

If a patient begins a new anti-tumor therapy within 28 days after the last administration of study medication, the SAE reporting period for SAEs ends at the time the new therapy is started.

The following information regarding SAEs should be captured by the site where possible:

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- Reason AE considered serious
- Date of hospitalization
- Date of hospital discharge
- Probable cause of death (if applicable)
- Date of death (if applicable)
- Autopsy performed (if applicable)
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication
- Causality assessment in relation to varlitinib/placebo
- Causality assessment in relation to capecitabine

The sponsor has a legal responsibility to notify the appropriate regulatory authorities about the safety of the study medication. Accordingly, the Investigator must report all SAEs per the definition stated in the protocol, regardless of presumed causal relationship, on the SAE page of the eCRF within 24 hours of becoming aware of the event. During eCRF downtime, the paper SAE form should be sent to the sponsor's assigned safety representative by email within 24 hours of becoming aware of the event.

Email: **ASLANSafety@parexel.com**

For medical emergencies contact:

Name: **Mei Ling Long**

Mobile: **+65 9888 9987**

Name: **Chih Yi Hsieh**

Mobile: **+886 975 865 105**

The Investigator should not wait to receive additional information to document fully the event before notification of a SAE, though additional information may be requested. Where applicable, information from relevant laboratory results, hospital case records, and autopsy reports should be obtained.

The sponsor and/or the sponsor's assigned safety representative will promptly notify all relevant Investigators and the regulatory authorities of findings that could adversely affect the safety of patients, impact on the conduct of the study or alter the IEC/institutional review board (IRB) approval/favorable opinion of the study. In addition, the sponsor's assigned safety representative, on behalf of the sponsor, will expedite the reporting to all concerned Investigators, to the IECs/IRBs, where required, and to the regulatory authorities of all adverse reactions that are serious, unexpected, and considered related to the study medication (See Section 7.1.1.1).

Details of the procedures to be followed if a pregnancy occurs are provided in Section 5.3.5.

7.1.1.3 Unexpected Adverse Reactions

Unexpected Adverse Reaction Definition

An unexpected adverse reaction is any untoward and unintended response that is related to the administration of the study drug at any dose that is not consistent with the applicable product information (e.g., Investigator's Brochure for an unauthorized investigational medicinal product or summary of product characteristics for an authorized product).

All suspected (i.e., related to the medication), unexpected serious adverse reactions (SUSARs) will be the subject of expedited reporting. The sponsor and/or the sponsor's assigned safety representative shall ensure that all relevant information about a SUSAR that is fatal or life-threatening is reported to the relevant competent authorities and IEC/IRB within 7 days after knowledge by the sponsor of such a case and that relevant follow-up information is communicated within an additional 8 days. All other SUSARs will be reported to the relevant competent authorities and IEC/IRB within 15 days after knowledge by the sponsor of such a case. All Investigators should follow up SUSARs until the event is resolved or until, in the opinion of the Investigator, the event is stabilized or determined to be chronic. Post study SUSARs that occur after the patient has completed the clinical study must be reported by the Investigator to the sponsor.

7.1.1.4 Clinical Laboratory Evaluation

The clinical laboratory tests specified below will be performed with the timing detailed in Table 1 (Safety lead-in) and Table 2 (Part 1 and Part 2). All clinical laboratory samples will be processed and evaluated by the site's local laboratory. Analysis of biomarkers will be performed by a central laboratory.

During the study, all out of range (abnormal) laboratory values must be evaluated and commented on by the Investigator for clinical significance. The clinical laboratory samples to be evaluated are presented in Table 13.

Table 13: Clinical Laboratory Parameters

Safety Clinical Laboratory Parameters (Using Local Laboratory)	
Hematology	Hemoglobin, hematocrit, red blood cell count, white blood cell, platelet count, white blood cell subset count (neutrophils, eosinophils, basophils, lymphocytes, and monocytes), mean corpuscular volume, mean corpuscular hemoglobin, mean cell hemoglobin concentration
Clinical Chemistry [fasted]	Albumin, total protein, blood glucose, sodium, potassium, blood urea nitrogen, creatinine, AST, ALT, alkaline phosphatase, gamma glutamyl transferase, total bilirubin, direct bilirubin, triglyceride, total cholesterol, lactate dehydrogenase, calcium, and uric acid
Liver Function Test	AST, ALT, alkaline phosphatase, gamma glutamyl transferase, total bilirubin, direct bilirubin
Coagulation	Prothrombin time/International Normalized Ratio, activated partial thromboplastin time
Urinalysis	Specific gravity, pH, protein, leucocytes, red blood cells, Nitrite, ketones, urobilinogen and bilirubin. Microscopy will be performed when necessary.
Pregnancy Screen	Females of childbearing potential will be screened for pregnancy. The screening pregnancy test will be by blood sample to detect the presence of β-HCG (collected as part of biochemistry sample). Serum or urine pregnancy tests are acceptable at subsequent visits at the Investigator's discretion.
Viral Serology	Hepatitis B surface antigen and Hepatitis B deoxyribonucleic acid viral load if Hepatitis B surface antigen returns positive, Hepatitis C virus antibody and human immunodeficiency virus antibody.
Tumor Markers – For Part 1 and Part 2 of the study only (Using Local Laboratory)	
Tumor Markers	CEA, CA19.9

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, β-HCG = beta human chorionic gonadotropin CA19.9 = cancer antigen 19.9, CEA = carcinoembryonic antigen.

Additional and repeat testing may be performed at the discretion of the Investigator.

All laboratory reports must be reviewed, signed, and dated by the Investigator.

Any clinical laboratory test result considered by the Investigator to be clinically significant should be considered an AE. Significant abnormal values that are drug-related occurring during the study will be followed until repeat test results return to normal, stabilize, or are no longer clinically significant.

7.1.1.5 Vital Signs

Blood pressure (systolic and diastolic), heart rate, respiratory rate, and temperature will be measured manually or automatically in a standardized manner in a sitting position after the patient has rested comfortably for 5 minutes.

7.1.1.6 Physical Examination

Physical examinations will be performed by a physician and/or delegated qualified personnel according to local legislation if applicable and will include the examination of the following: general appearance, eyes, ears, nose, throat, chest/respiratory, heart/cardiovascular, gastrointestinal/liver, musculoskeletal/extremities, dermatological/skin, thyroid/neck, lymph nodes, and neurological/psychiatric systems.

The patients' height will be checked at screening visit, and body weight will be checked at the start of each cycle during the study.

All clinically significant treatment-emergent findings that were not present at baseline or described in the medical history will be recorded as AEs.

7.1.1.7 12-lead ECG

A 12-lead ECG will be taken in the supine position, after the patient has been lying down for at least 10 minutes in a quiet environment. There should be no significant external stimulation (TV, radio, interaction with other subjects). Detailed instructions, including the allowable window of time to complete the ECGs, will be described in the ECG manual. The ECG machines supplied by the Core ECG Laboratory will be used for all ECG collection, and the digital files of each tracing will be archived.

<u>General Principles (Safety Lead-in and Part 1)</u>

The following parameters will be assessed: heart rate, PR, QRS, QT, QTcF (Fridericia's formula), and QTcB (Bazzett's formula). While the Investigator (or a qualified observer at the investigational site) will interpret the ECG using one of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant, the final ECG assessments (including interval measurements) will be made by the Core ECG laboratory.

Baseline will be defined as the mean of the triplicate QT/QTc readings performed pre-dose on Day 1. On Day 1, pre-dose is defined as 2 sets of triplicate ECGs taken 45 minutes

and 5 minutes prior to dosing. The ECG values from these 2 sets of ECGs will be averaged to create the baseline values. Similarly, for all other time points, for each ECG parameter, each patient's mean will be calculated from the triplicate readings and the mean value will be used.

Safety Lead-In

Any analysis of ECG data from the Safety lead-in is considered exploratory.

On Cycle 1 Day 1 and Day 8, the following parameter will be determined at the following time points:

- Absolute heart rate, pulse rate, QRS, QT/QTc values at 45 minutes pre-dose, 5 minutes pre-dose, 1, 2, 3, 4, 5, 6 8.5, and 12 hours post dose
- Heart rate, pulse rate, QRS, QT/QTc change from baseline at 1, 2, 3, 4, 5, 6, 8.5, and 12 hours post-dose

QTc will be reported for both Fridericia and Bazett's corrections.

Triplicate ECGs will also be collected 3 hours post-dose Day 22 (Cycle 2 Day 1) and onwards every cycle while the subject remains in the study.

Due to the non-randomized, open label design of the Safety lead-in, data from the Safety lead-in will be presented separately from data from Part 1 of the study. Furthermore, ECG/QT outputs will be made available to the DSMB for consideration when determining whether the study should progress to Part 1.

Part 1

The Part 1 electrocardiographic Core ECG Laboratory assessments constitute the study's primary assessment of ECG/QTc. The time-based electrocardiographic analysis will be performed in Part 1 at baseline, Cycle 1 Day 1, Cycle 1 Day 8, and safety follow-up visit.

On Cycle 1 Day 1 and Day 8, the following parameters will be determined at the following time points:

- Absolute heart rate, pulse rate, QRS, and QT/QTc values at 45 minutes pre-dose, 5 minutes pre-dose, 1.5, 3, 5, 8 hours post-dose.
- Heart rate, pulse rate, QRS, and QT/QTc change from baseline at 1.5, 3, 5, and 8 hours post-dose.

Twenty-eight days after the last dose of study drug (after full drug washout), a set of triplicate ECGs will be collected 3 hours after a light snack.

In addition, triplicate safety ECGs will be collected 3 hours post-dose on Day 22 (Cycle 2 Day 1), Day 64 (Cycle 4 Day 1) and every 2 cycles while the subject remains in the

study. This data will not be analyzed by the Core ECG Laboratory but will be assessed by the investigator.

Part 2

ECGs will be collected in Part 2 of the study as part of standard safety monitoring at screening, baseline (before a snack), and 3 hours post-dose on Day 22 (Cycle 2 Day 1), Day 64 (Cycle 4 Day 1) and every 2 cycles while the subject remains in the study. These data will not be analyzed by the Core ECG Laboratory but assessed by investigators.

7.1.1.8 ECOG Performance Status

The ECOG performance status will be recorded using the scale provided in Appendix 14.2.

7.1.2 Efficacy Variables

7.1.2.1 Tumor Evaluation

Tumor evaluations will be performed to evaluate the efficacy of treatment according to RECIST version 1.1 (Appendix 14.1). Tumor response will be assessed by means of computed tomography (CT) or magnetic resonance imaging (MRI) at baseline and every 6 weeks from Cycle 1 Day 1 during the treatment period until EOT (Safety Lead-in) or disease progression (Part 1 and Part 2).

Baseline CT/MRI of the chest, abdomen, and pelvis images must be performed within 21 days prior to Cycle 1 Day 1, brain and/or bone lesions may be scanned if applicable.

For Part 1 and 2 of the study, radiological assessments should continue until the patient experiences disease progression, regardless of whether the patient discontinues randomized therapy or starts a subsequent anti-cancer therapy.

All tumor responses should be assessed at every assessment time point using the same methods (contrast-enhanced CT or MRI) used to characterize the lesions identified at baseline. Apart from the radiological reading at the site to determine disease progression, for Part 1 of the study all images will be assessed by a blinded ICR, and the ICR must confirm the presence of measurable disease in order to confirm a patient's eligibility at baseline screening prior to a patient being randomized into the study. Central radiological reading will not interfere with Investigator's judgment on disease progression.

For Part 1 only, the co-primary endpoints of ORR and PFS and other secondary endpoints (except OS) will be based on the blinded ICR of all radiological data. Objective response rate as determined by the site review will also be reported as a secondary endpoint.

7.1.2.2 Cancer Antigen Evaluation

For Part 1 and 2 of the study, blood will be collected for analysis of CA19.9 and carcinoembryonic antigen (CEA) at screening and every 6 weeks (±5 days) from Cycle 1 Day 1. Collection of blood for these analysis stops at EOT.

Archival paraffin-embedded tumor tissues will be collected during screening for future analysis if the patient has provided the optional tumor tissue consent.

Biopsies will be performed during screening for those patients who did not have enough archival tumor tissue if the patient has provided the optional tumor tissue consent.

7.1.3 Pharmacokinetic Variables

7.1.3.1 Determination of Drug Concentrations in Biological Samples

Safety Lead-in Part

Analysis of plasma samples for the determination of varlitinib (and any relevant circulating metabolites), capecitabine and 5-FU will be performed in Safety Lead-in Part. Other relevant circulating metabolites of capecitabine (5'-DFCR, 5'-DFUR and FBAL) will only be determined if this is considered necessary based on the pharmacokinetic and safety findings of the study. Relevant circulating metabolites of varlitinib will not be determined at this Safety Lead-in because they remain unknown.

Part 1 and 2

Analysis of plasma samples for the determination of varlitinib and its relevant circulating metabolites will be performed in Part 1 and Part 2. Capecitabine and 5-FU will not be determined in Parts 1 and Part 2 of the study if no relevant pharmacokinetic interactions between varlitinib and capecitabine/5-FU are observed in the Safety Lead-in part of the study.

7.1.3.2 Pharmacokinetic Sampling

Safety Lead-in

Blood samples for PK analysis of varlitinib (and any relevant circulating metabolites), capecitabine, and 5-FU (active capecitabine metabolite) will be collected at the following time points in the Safety lead-in part only:

- Cycle 1 Day 1: 5 minutes pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8.5, 10, and 12 hours post-dose
- Cycle 1 Day 8: 20 minutes pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8.5, 10, and 12 hours post-dose

- Cycle 1 Day 14: 5 minutes pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8.5, 10, and 12 hours post-dose

Patients must withhold taking the morning dose of varlitinib and capecitabine until pre-dose PK sample is collected. The actual sample date and time of all PK samples must be recorded in the CRF.

In addition, unscheduled PK collected 7 days following dose reduction of varlitinib at any cycle of treatment: up to 5 minutes pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8.5, 10, and 12 hours post-dose if required.

Part 1 and Part 2

In Part 1 and Part 2, PK samples will be obtained for the PK evaluation of varlitinib (and any relevant circulating metabolites). PK samples will be collected at the following time points:

Part 1 (All patients)
- Cycle 1 Day 1: 5 minutes pre-dose, 1.5, 3, 5, and 8 hours post-dose
- Cycle 1 Day 8: 20 minutes pre-dose, 1.5, 3, 5, and 8 hours post-dose
- End of study after full drug washout: 28 days after last dose at the patient's safety follow-up visit

Part 2 (Sparse Sampling)
- Cycle 1 Day 1: 5 minutes pre-dose, 1-3 hours post-dose, 3-5 hours post-dose, and 5-8 hours post-dose
- Cycle 2 Day 1: 20 minutes pre-dose, 1-3 hours post-dose, 3-5 hours post-dose, and 5-8 hours post-dose

In order to maintain the double-blind design of the study, blood samples will be collected from all subjects in Part 1 for plasma measurements of varlitinib and its potential relevant circulating metabolites. For the sparse PK sampling in Part 2, the double-blind design will also be maintained and blood samples will be collected for a selected number of subjects, without limiting the sampling to the varlitinib subjects only.

All PK data will be analyzed according to treatment received. Deviations that have the potential to significantly affect the PK will be reviewed. The population, and decisions regarding which profiles are usable, will be defined by the Study Team Physician, Pharmacokineticist, and Statistician prior to any analyses being performed.

In addition, unscheduled PK samples will be collected at least 7 days following dose reduction of varlitinib at any cycle of treatment: up to 5 minutes pre-dose and 3-5 hours post-dose.

Handling and processing details, including the allowable window of time to complete the PK blood draws, will be outlined in the Laboratory Manual.

7.1.3.3 Pharmacokinetic Analysis

Safety Lead-in

The PK of varlitinib (and any relevant circulating metabolites), capecitabine and 5-FU (active metabolite) will be determined at selected time points. The following PK parameters will be evaluated where possible:

Cycle 1 Day 1, Day 8, and Day 14:

- maximum plasma concentration (C_{max})
- time to C_{max}(t_{max})
- plasma concentration before next dose (C_{trough})
- area under the plasma concentration-time curve from 0 to 12 hours ($AUC_{0-\tau}$)
- half-life ($t_{1/2}$)
- apparent clearance (Cl/F)
- apparent volume of distribution (V_z/F)
- apparent volume of distribution at the steady state (V_{ss}/F)

where τ = 12 hours (dosing interval)

Cycle 1 Day 8

- accumulation ratio of $AUC_{0-\tau}$ ($RacAUC_{0-\tau}$) (Day 8/Day 1)
- accumulation ratio of C_{max} $RacC_{max}$ (Day 8/Day 1)

Cycle 1 Day 14

- accumulation ratio of $AUC_{0-\tau}$ ($RacAUC_{0-\tau}$) (Day 14/Day 1)
- accumulation ratio of C_{max} $RacC_{max}$ (Day 14/Day 1)

Summary statistics for varlitinib (and any relevant circulating metabolites) will be tabulated for the PK parameters by study day. The mean, standard deviation (SD), coefficient of variation (%CV), geometric mean, %CV geometric mean, median, minimum, and maximum will be presented for relevant PK parameters indicated above. Median, minimum, and maximum will be presented for T_{max}. Profile plots of patient data will be presented on both linear and log scale.
Pharmacokinetic parameters in plasma will be derived using standard non-compartmental methods with WinNonlin® Professional Version 5.2 or higher (Pharsight Corp., Mountain View, California, US) or SAS® Version 9.2 or higher (SAS Institute, Inc., Cary, North Carolina, US). Actual elapsed time from dosing will be used for final plasma PK parameter calculations.

Part 1 and Part 2

Using appropriate PK software depending on whether comprehensive PK sampling or sparse PK sampling is obtained in practice, the PK data will be used to derive PK parameters such as, but not restricted to, C_{max}, AUC, and $t_{1/2}$ for varlitinib.

Population PK evaluation in Part 1 and Part 2 of the study will be performed by nonlinear mixed effects model (NLME) using NONMEM program version VII (Globomax LLC, Ellicott City, MD, US) and SAS® Version 9.2 or higher (SAS Institute, Inc., Cary, North Carolina, US). Actual elapsed time from dosing will be used for final plasma PK parameter calculations.

The final PK analyses will be the responsibility of the CRO. Pharmacokinetic analyses will be conducted according to CRO Standard Operating Procedures (SOPs) for PK analyses unless otherwise specified. The actual PK sampling times will be used in the PK calculations.

The varlitinib concentration-time profiles, along with the derived PK variables, will be listed for each patient per dose and dosing day and summarized appropriately. Population PK models may be used to derive the PK parameters and will aim to characterize variability in the population by investigating the influence of covariates such as weight, age, smoking status and/or concomitant medications. In addition, if the data are suitable, potential relationships between plasma varlitinib and efficacy or safety endpoints will be investigated using a graphical approach and/or appropriate PK/PD modeling techniques.

7.1.4 Biomarker Variables

Blood samples for retrospective analysis of potential biomarkers will be collected at baseline and post week 6 treatment tumor assessment.

For Part 1 and 2 of the study, optional donation of archival/fresh tumor biopsy samples can be provided (a separate consent to be signed). The minimum archival tumor tissue to be collected is 19 unstained slides of 5 microns. The collected tumor tissue and blood samples, as well as, matched normal tissue will be stored for further analyses for mRNA, proteins and genes.

Refer to the Bioanalytical Laboratory Manual for detailed sample collection, labeling, storage, and shipment instructions for further analysis of tumor tissues.

Exploratory variables will be evaluated in Part 1 only.

Possible relationships between protein and phospho-protein expression levels and clinical outcome, and gene mutational status and clinical outcome will be explored using proteins and genes including, but not limited to:

- Via IHC:
  - epidermal growth factor receptor (EGFR), pEGFR

  - HER2, pHER2
  - HER3, pHER3
  - HER4, pHER4
- Via PCR/Sequencing
  - Mutational status of genes, such as *KRAS, NRAS, BRAF*, *EGFR, HER2* and other genetic factors that may affect response to therapy.

The protein and gene studies will be conducted using archival material (and if not available, biopsy tissue samples).

If a relationship is found between biomarker(s) expression and clinical outcomes in Part 1 of the study, the biomarker(s) could be prospectively evaluated in Part 2 of the study.

7.2 Data Safety Monitoring Board and Independent Central Review

A DSMB consisting of independent experts will be convened on 2 specified occasions to review the accumulating safety date for the study.

The first DSMB meeting will occur after the first 12 patients in the Safety lead-in have completed the 21 days of follow-up, and before initiating Part 1 of the study.

The second DSMB meeting will occur at a selected time point during Part 1 of the study according to DSMB Charter.

The composition, specific responsibilities, scope and plan of the DSMB will be defined in the DSMB Charter.

Radiological images collected in the Part 1 of the study will be assessed by ICR. Details of the ICR will be defined in the ICR Charter.

8 STATISTICAL ANALYSIS

8.1 General Statistical Considerations

All statistical analyses will be performed by the designated CRO, using SAS®, version 9.3 or higher.

Unless specified otherwise, data from the Safety lead-in, Part 1, and Part 2 of the study will be presented separately in the tables, figures, and listings. Patients whose data contributed to the Part 1 analysis will not be included in the Part 2 analysis.

For Parts 1 and 2, for the purpose reporting all FAS and EFR--based endpoints (efficacy data and demography), *Study Day* 1 is defined as the date of randomization to study treatment. For visits (or events) that occur on or after randomization, study day is defined as (date of visit [event] -date of randomization + 1). For visits (or events) that occur prior to randomization, study day is defined as (date of visit [event] -date of randomization). There is no Study Day 0.

For Parts 1 and 2, for the purpose of reporting all safety set based endpoints (e.g. AEs, laboratory findings, vital signs, ECG, exposure and dose intensity) and PK set-based endpoints, *Dose Day* 1 is defined as the date of first dose of study treatment (referred to in the protocol as Cycle 1 Day 1). For visits (or events) that occur on or after first dose, dose day is defined as (date of visit [event] -date of first dose of study treatment + 1). For visits (or events) that occur prior to first dose, dose day is defined as (date of visit [event] -date of first dose of study treatment). There is no Dose Day 0. For listings (such as for AEs) that include the derivation of "days since last dose," this is defined as (event date -date of last dose). Events that occur on the same day as the last dose of study drug will therefore be described as occurring zero days from the last dose of study drug.

The database for the Safety lead-in will be locked at the time of the Part 1 analyses. However, interim data from the Safety lead-in will be made available to the DSMB prior to the final DCO to enable the DSMB to review the emerging safety and tolerability data and to advise whether the study can proceed to Part 1. Details of the data to be provided to the DSMB will be provided in the DSMB charter.

The primary analysis of Part 1 will be the later of 3 months after last Patient in or when 70% of the patients (84 patients) have experienced a PFS event. The primary analysis of all primary and secondary endpoints, with the exception of OS, will be performed at this time.

For Part 1, a preliminary analysis of OS will be performed at the time of the primary analysis of ORR and PFS. It is anticipated that the OS data at this time will be immature, thus a second analysis of OS is planned for when approximately 95 patients (approx. 79%) have an OS event. The second analysis of OS will be considered the primary analysis of OS for the trial.

The DCO for Part 2 will be when 247 OS events have occurred. All secondary endpoints, including ORR, PFS and DoR, will be reported at the time of the primary analysis of OS.

8.2 Sample Size Derivation

8.2.1 Safety Lead-in Sample Size

The Safety lead-in is not formally powered to assess any statistical hypotheses. In this part, 12 to 20 eligible patients (6-12 from US, 6-8 from ROW) will be enrolled to receive varlitinib plus capecitabine.

Patients in this group will be replaced if study medication compliance is < 85% in the first 14 days.

8.2.2 Part 1 Sample Size

Part 1 is designed with co-primary endpoints ORR and PFS. In order to maintain an overall, 1-sided 10% type I error rate for Part 1, a Hochberg procedure[15] will be used, such that the study will be deemed to have met its primary objective if either endpoint is significant at the 1-sided 5% level or if both endpoints are significant at the 1-sided 10% significance level.

One hundred and twenty patients provide approximately 80% power to detect a true difference of 17% in response rate, based on a 1-sided 5% significance level and assuming 10% response rate for the placebo group and a 27% response rate for varlitinib. To ensure the adequate data are available to evaluate the effects of varlitinib on both co-primary endpoints, the DCO for the primary analysis will be the later of 3 months after last patient in and when 70% of patients (84 patients) have experienced a PFS event. Based on a minimum of 84 PFS events at the time of the primary analysis, the study would have a minimum of 80% power to detect a true HR of 0.58 for PFS based on a 1-sided 5% significance level.

Furthermore, if the primary objective of the study is met, the following approach to type I error control will be applied in order to support marketing approval:

- The overall type I error rate for marketing approval will be controlled at the two-sided 5% level, using a Hochberg procedure

- Using this approach, statistical significance may be claimed if *either* ORR or PFS is significant at the two-sided 2.5% significance level or if *both* ORR and PFS are significant at the two-sided 5% significance level.

One hundred and twenty patients provide approximately 80% power to detect a true difference of 20% in response rate, based on a 2-sided 5% significance level and assuming 10% response rate for the placebo group and a 30% response rate for varlitinib.

A total of 84 PFS events provides 80% power to detect a true HR of 0.54, based on a two-sided 5% significance level. Assuming a 8-month non-linear recruitment period, a 2.67 month median PFS for capecitabine alone, and a true HR of 0.54, it is estimated that the DCO for the primary analysis of Part 1 will occur approximately 12 months after the first patient is randomized into the study (first patient in).

Overall Survival is a secondary endpoint in Part 1. A preliminary analysis of OS will be performed at the time of the primary analysis of ORR and PFS. It is anticipated that the OS data at this time will be immature, thus a second analysis of OS is planned for when approximately 95 patients (approx. 79%) have an OS event. Due to the number of OS events expected at the time of the first analysis, this initial analysis of OS will be considered exploratory only. Although a p-value may be presented, for the purpose of marketing authorization, no claims of statistical significance will be based on the initial analysis. For the purpose of type I error control across the two analyses of OS in support of marketing authorization, the OS update analysis will be considered the primary analysis of OS for Part 1 of the study, and statistical significance will be assessed at the two-sided 5% significance level.

8.2.3 Part 2 Sample Size

Part 2 is designed with a primary endpoint of OS. Approximately 350 patients will be randomized into Part 2 to obtain 247 death events (70% maturity). If the true OS HR for the comparison of varlitinib+capecitabine versus placebo+capecitabine is 0.7 (likely to correspond to a 43% prolongation of OS), the study has 80% power to demonstrate a statistically significant difference for OS, assuming a 2-sided 5% significance level.

Assuming non-linear recruitment of 350 patients over a twenty-four month period, and median OS times of 8.6 months and 6 months for the varlitinib and placebo arms respectively, it is estimated that 247 OS events will occur approximately 31 months after the first patient in for Part 2.

All secondary endpoints will be analyzed at the time of the primary analysis of OS.

8.3 Analysis Populations

8.3.1 Safety Population

For each part of the study, the safety population includes all patients in that part of the study who received at least 1 dose of randomized therapy (or study medication in the Safety lead-in) and will be the primary analysis set for the assessment of safety and tolerability in the study.

For the purpose of data summaries, patients will be included in the safety population according to the treatment arm and dose level initially received, regardless of any subsequent dose adjustments.

8.3.2 Full Analysis Set

For each part of the study, the full analysis set is based on the intention-to-treat principle and includes all randomized patients (or treated patients for the Safety lead-in) analyzed in accordance with the intended treatment arm, regardless of the treatment actually received.

With the exception of Part 1, Tumor Size which is not considered a key secondary endpoint (See Section 8.4.6 and 8.5.2.1), for all study parts, the primary analysis of all primary and key secondary efficacy endpoints, will be based on the full analysis set (FAS).

8.3.3 Evaluable for Response Set (Part 1 only)

The EFR set is defined as a subset of the FAS and includes patients with measurable disease at baseline, as determined by ICR assessments of radiological data based on the RECIST criteria, version 1.1. For Part 1 only, a sensitivity analysis of ORR and DCR will be performed in the evaluable for response (EFR) set to investigate the impact of patients without measurable disease on the primary endpoint. Since measurability is an inclusion criteria, all patients in Parts 1 should have measurable disease at baseline. Thus, if no patients were randomised in error, results in the EFR set will not be presented.

Since tumor size is an endpoint based on patients' tumor measurements, it can only be defined for the subset of the FAS with measurable disease at baseline. Thus the EFR set will be the primary analysis set used for the assessment of tumor size for Part 1 (See Section 8.4.6).

8.3.4 Per Protocol Analysis Population

The per protocol (PP) analysis population is defined for Part 1. Efficacy is not the focus of the Safety lead-in and Part 2 will be assessed on an intention-to-treat basis only. Thus PP analyses are not required for the Safety lead-in and Part 2 of the study.

The PP analysis population will include all randomized patients according to the treatment actually received, and excluding any patients with major deviations. Major deviations that would lead to exclusion from the PP analysis population include:

- Patients who did not have the intended disease (failure of inclusion criteria 2)
- Subjects who did not have the intended indication, i.e. were not second line patients (failure of inclusion criteria 3)
- Patients who did not received any randomized therapy
- Patients with baseline radiological scan performed before the start of protocol-specified interval prior to randomization
- Patients who did not have measurable disease at baseline as determined by ICR
- Subjects who have not received at least six doses of gemcitabine in a first line setting (i.e. failure of inclusion criteria 4, protocol version 4.0 onwards)

- Subjects with multiple (≥2) peritoneal metastases at baseline or ascites at baseline which cannot be attributed to a non-malignant cause (i.e. failure of exclusion criteria 3, protocol version 4.0 onwards), based on ICR review
- Subjects with baseline albumin <3 g/dL (failure of the albumin component of inclusion criteria 9c)

In addition to the programmatic determination of the major deviations, monitoring notes or summaries will be reviewed to determine any important post entry deviations that are not identifiable via programming, and to check that those identified via programming are correctly classified. The final classification will be made blinded, prior to database lock.

Patients who received the incorrect randomized therapy should be included in the PP analysis set according to the therapy actually received. Similarly, subjects who were mis-stratified at randomization will be included in the PP analyses according to the correct stratification levels, regardless of the levels declared at randomization.

Failure of an inclusion/exclusion criterion will not automatically be classified as a major deviation.

The PP analysis population will be the used to assess the sensitivity of the Part 1 ORR, DoR, DCR, PFS and OS analyses to major deviations.

8.3.5 PK Analysis Set

The PK population contains all patients who have been dosed with varlitinib and provided at least one usable PK profile. All PK data will be analyzed according to treatment received.

For the Safety lead-in, this population will comprise all data patients who receive study treatment as per protocol (300 mg BID) and did not violate or deviate from the protocol and planned dosing regimen (300 mg) in ways that would significantly affect the PK analyses (for example skipping doses, or taking reduced doses or taking concomitant medications with the potential to cause a drug-drug interaction) during the PK sampling period. Patients who did deviate from the planned dosing regimen may still provide some data for inclusion in the PK set if they have at least one usable PK profile. The population, and decisions regarding which profiles are usable, will be defined by the Study Team Physician, Pharmacokineticist, and Statistician prior to any analyses being performed.

PK sampling of all patients is planned for Part 1 the study, while sparse PK sampling is planned for Part 2. The number of patients who will provide samples in Part 2 for the PK analysis will be defined based on the results of Part 1 of the study. All PK data will be analyzed according to the treatment received. Deviations that have the potential to significantly affect the PK will be reviewed, and patients, or specific PK profiles for a patient, may be excluded from the PK set if appropriate. The population, and decisions regarding which profiles are usable, will be defined by the Study Team Physician, Pharmacokineticist, and Statistician. Since the PK sample analysis may be performed following the primary analyses of efficacy, the CRO responsible for the analysis of the

PK samples will mask the subject ID prior to any discussion regarding deviations, in order to ensure that decisions regarding which samples to include/exclude from the PK set are made blinded to clinical outcomes.

Population PK models may be used to derive the PK parameters.

Table 14: Summary of Outcome Variables and Analysis Populations

Outcome Variable	Analysis Population (Sensitivity Analysis Population)
Efficacy Data *(Primary and key secondary endpoints)*	
ORR, DCR	FAS (EFR and PP Part 1 only)
PFS, OS, DoR	FAS (PP Part 1 only)
Part 1 ORR based on site data	FAS
Part 1 Tumor size[1]	EFR
Demography	FAS
Pharmacokinetics	
PK	PK
Safety	
Exposure	Safety
Adverse Events	Safety
Laboratory measurements	Safety
Vital Signs	Safety
ECG	Safety
Physical Examination	Safety

1 Tumor size, by definition, is only defined in patients with measurable disease. For marketing authorization, no statistical claims will be based on tumor size (See Section 8.5.2.1).

Abbreviations: DCR = disease control rate, DoR = duration of response, ECG = electrocardiogram, EFR = evaluable for response, FAS = full analysis set, ORR = objective response rate, OS = overall survival. PFS = progression- free survival, PK = pharmacokinetics, PP = per protocol

8.4 Study Endpoints

8.4.1 Objective Response Rate

Objective response rate is a co-primary endpoint in Part 1 and a secondary endpoint in Part 2, and the Safety lead-in cohort.

Objective response rate is defined as the number (%) of patients with at least one visit response of CR or PR. Data obtained up until progression, or last evaluable assessment

in the absence of progression, will be included in the assessment of ORR. This will be irrespective of whether or not patients discontinued treatment or received a subsequent therapy prior to progression. For all study parts, ORR will be evaluated based on the FAS set (Section 8.3.2).

8.4.2 Progression-Free Survival

Progression-free survival is a co-primary endpoint in Part 1, and is a secondary endpoint in Part 2.

Progression-free survival is defined as the time from randomization (or start of treatment in the Safety lead-in) until the date of objective disease progression or death (by any cause in the absence of disease progression) regardless of whether the patient withdraws from randomized therapy (study treatment in the Safety lead-in) or receives another antitumor therapy prior to disease progression. Patients who have not experienced disease progression or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment. However, if the patient progresses or dies after 2 or more missed visits, the patient will be censored at the time of the latest evaluable RECIST version 1.1 assessment.

The PFS time will always be derived based on the scan/assessment dates rather than visit dates and the following rules will be applied:

- Date of disease progression will be determined based on the earliest of the dates of the component that triggered the disease progression, i.e., if both the target lesions and the non-target lesions indicate disease progression but were scanned on different days, the earlier of the 2 dates would be applied.

- When censoring a patient for PFS, the patient will be censored at the latest of the dates contributing to a particular overall visit assessment.

For Part 1, the co-primary endpoint, PFS, will be derived programmatically using data from the ICR. To support sensitivity analyses, PFS will also be derived programmatically using the site assessments of the Part 1 radiological data.

For Part 2 and the Safety lead-in, PFS will be derived programmatically using the site radiological data.

Further details will be provided in the SAP.

8.4.3 Overall Survival

Overall survival is a secondary endpoint in Part 1, and the primary endpoint in Part 2 of the study.

Overall survival is defined as the time from the date of randomization until death due to any cause. Any patient not known to have died at the time of DCO will be censored based on the last recorded date on which the patient was known to be alive.

Note, survival calls may be made in the week following the date of DCO for the analysis, and if patients are confirmed to be alive or if the death date is after the DCO these patients will be censored at the date of DCO.

8.4.4 Duration of Response

Duration of response is secondary endpoint in all study parts.

The DoR is defined as the time from the date of first documented response until the date of documented disease progression or death in the absence of disease progression. The end of response should coincide with the date of disease progression or death from any cause used for the PFS endpoint. For Part 1, DoR will be calculated using the ICR data, and for Part 2 and the Safety lead-in, DoR will be calculated from the site radiological data.

The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR. For example, if the patient was first noted to have a PR at week 6, and the target and non-target lesions were assessed on different dates at this visit, then the later of the 2 assessment dates would be used as the start date of the response.

If a patient does not progress following a response, then their DoR will use the PFS censoring time.

Duration of response will not be defined for those patients who do not have documented response.

8.4.5 Disease Control Rate

Disease control rate is a secondary endpoint in all study parts.

Disease control rate is defined as the number (%) of patients with at least one visit response of CR or PR, or with stable disease for a minimum of twelve weeks (± 5 days) from randomization (Parts 1 and 2) or starting treatment (Safety lead-in only). Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of DCR. This will be irrespective of whether or not patients discontinued treatment or received a subsequent therapy prior to progression. For all study parts, DCR will be evaluated based on the FAS set (Section 8.3.2). For Part 1, DCR will be calculated based on the ICR data. For Part 2 and the Safety lead-in, DCR will be calculated from the site radiological data.

8.4.6 Tumor Size

The percentage change from baseline in tumor size at Week 12 ($\%\Delta TS_{Wk12}$) is a secondary endpoint for Part 1, and will be used to help evaluate the exploratory objectives of investigating the possible role of baseline biomarker levels as predictors of clinical benefit. It will be evaluated using the Evaluable for Response set (EFR) (Section 8.3.3). Tumor size is not considered to be a key secondary endpoint; for the purpose of marketing authorization, no statistical claims will be made based on tumor size.

The $\%\Delta TS_{Wk12}$ will be defined as follows:

- Baseline tumor size: defined as the sum of longest diameters of target lesions at baseline
- Week 12 TS: defined as the sum of longest diameters of target lesions at week 12

$$\%\Delta TS_{Wk12} = 100 \times \frac{Week\ 12\ TS - Baseline\ TS}{Baseline\ TS}$$

An increase from baseline of 20% will be imputed for any patients who die by any cause, or withdraw from the study due to symptomatic disease progression prior to Week 12. Any patients who withdraw from the study due to radiological disease progression prior to Week 12 will be included in the analysis, and will be assigned a percentage change from baseline of 20%, or the value that was observed at the time of disease progression (whichever is larger). Full details of data imputation rules will be provided in the SAP.

8.4.7 Safety Endpoints

Patient safety will be evaluated based on physical examination, vital signs (blood pressure [systolic and diastolic], heart rate, respiratory rate, and body temperature), ECG parameters, clinical laboratory tests (hematology, clinical chemistry, coagulation, and urinalysis), and AEs.

8.4.8 ECG Parameters

The ECG parameters of interest are QT including QTcF and QTcB, HR (heart or ventricular rate), PR, and QRS intervals.

8.5 Methods of Statistical Analysis

8.5.1 Primary Endpoints

8.5.1.1 Part 1 - Objective Response Rate

The primary analysis will test for the superiority of varlitinib-containing treatment arm relative to the placebo-containing arm.

Objective response rate will be analyzed using a stratified exact binomial test [16,17] that extends Fisher's Exact test to more than one stratum. The analysis will be stratified by

primary tumor location (gallbladder/NonGB). The 2-sided p-value will be obtained by doubling the 1-sided p-value.

The conditional maximum likelihood estimate of the odds ratio will be presented together with its exact 2-sided 95% confidence limit, which excludes one if and only if the stratified exact binomial test is significant at a 2-sided 5% level. Corresponding significance levels and confidence intervals (CIs) will be calculated using tests performed at a 1-sided 10% level. The 1-sided p-value will also be presented.

To test for heterogeneity across strata, the exact test of Zelen[18] will be performed testing whether the treatment effect differs between the 2 strata included in the primary analysis.

For Part 1 only, subgroup analyses will be conducted comparing ORR between treatments in the subgroups of the FAS set defined by the stratification factors declared at randomization, Region (US/Non-US) and primary tumor location (GB/Non-GB), plus the following factors:

- Gender (male vs female)
- Race (Asian/Caucasian/Other)
- Baseline ECOG status (0/1)
- Extent of disease (locally advanced/metastatic)
- Age (<60/>=60)
- Baseline HER2 expression (positive defined as +++ or above by IHC, otherwise negative)
- Any HER positivity (positive defined as + or higher by IHC for HER1, HER2, HER3, HER4, or otherwise negative)

Note: The sub-group analyses based on IHC biomarker data will be reported outside of the main CSR.

Other baseline variables may also be included if there is clinical justification or an imbalance is observed across the treatment arms. For each sub-group, the odds ratio and corresponding 80% CI will be presented on a forest plot including the odds ratio and 80% CI from the overall population. Additionally, if the primary analysis of ORR is significant at the 2-sided 5% level in the overall population, the forest plot will be replicated using 95% CI.

No adjustment to the significance level for testing will be made since all these analyses will be considered supportive of the primary analysis of ORR.

8.5.1.2 Part 1 – Progression-Free Survival

In Part 1, the primary analysis will test for the superiority of varlitinib-containing treatment arm relative to the placebo-containing arm, as assessed by PFS. The DCO for the primary analysis of PFS will be the later of 12 weeks after last patient in and 84th documented PFS event.

Progression-free survival will be analyzed using a stratified log-rank test using the Breslow method to handle ties.[19] The stratification factor is primary tumor location (GB/Non-GB). The results will be presented in terms of the HR (with a HR <1 favoring the varlitinib-containing arm) and associated 2-sided 95 CI and 2-sided p-value. For Part 1 only, the 80% CI and 1-sided p-value will also be presented. The HR and its CI can be estimated from the log-rank as follows[20,21,22]:

$HR = \exp(U/V)$

95% CI for $HR = (\exp\{U/V - 1.96/\sqrt{V}\}, \exp\{U/V + 1.96/\sqrt{V}\})$

Where $U = \sum_k U_k = \sum_k \sum_i (d_{1ki}, -e_{1ki})$ is the stratified log-rank test statistic obtained from the SAS LIFETEST procedure, $\sqrt{V} = \sqrt{\sum_k V_k}$, is its standard deviation, k denotes the stratum and d_{1ki} and e_{1ki} are the observed and expected events in group 1, stratum k.

Kaplan-Meier (KM) plots of PFS, with tick marks to identify censored observations, will be presented by treatment group. Summaries of the number and percentage of patients experiencing a PFS event, and the type of event (RECIST 1.1 or death) will be provided along with median PFS for each treatment.

The assumption of proportionality will be assessed.

For Part 1 only, subgroup analyses will be conducted comparing PFS between treatments in the subgroups of the full analysis set defined by the stratification factors declared at randomization, Region (US/Non-US) and primary tumor location (GB/Non-GB), plus the following factors:

- Gender (male vs female)
- Race (Asian/Caucasian/Other)
- Baseline ECOG status (0/1)
- Extent of disease (locally advanced/metastatic)
- Age (<60/>=60)
- Baseline HER2 expression (positive defined as +++ or above by IHC, otherwise negative)
- Any HER positivity (positive defined as + or higher by IHC for HER1, HER2, HER3, HER4, or otherwise negative)

Note: The sub-group analyses based on IHC biomarker data will be reported outside of the main CSR.

Other baseline variables may also be assessed if there is clinical justification. For each subgroup, the HRs (varlitinib: placebo) and associated CIs will be calculated from a log rank test within each individual subgroup. These will be presented on a forest plot including the HR and 80% CI from the overall population. The purpose of the subgroup

analyses is to assess the consistency of treatment effect across expected and possible prognostic factors.

No adjustment to the significance level for testing will be made since all these analyses will be considered supportive of the primary analysis of PFS.

For both Part 1 and Part 2, Cox proportional hazards modeling will be employed to assess the effect of covariates on the HR estimate. Before embarking on more detailed modeling, an initial model will be constructed, containing treatment and the stratification factor primary tumor location alone, to ensure any output from the Cox modeling is likely to be consistent with the results of the stratified log-rank test.

The presence of quantitative interactions will be assessed formally by means of an overall global interaction test. This will be performed in the full analysis set by comparing the fit of a Cox proportional hazards model including treatment, all covariates, and all covariate-by treatment interaction terms, with one that excludes the interaction terms and will be assessed at the 2-sided 10% significance level. If the fit of the model is not significantly improved then it will be concluded that overall the treatment effect is consistent across the subgroups.

If the global interaction test is found to be statistically significant, an attempt to determine the cause and type of interaction will be made. Stepwise backwards selection will be performed on the saturated model, whereby (using a 10% 2-sided level throughout) the least significant interaction terms are removed one-by-one and any newly significant interactions re-included until a final model is reached where all included interactions are significant and all excluded interactions are non-significant. Throughout this process all main effects will be included in the model regardless of whether the corresponding interaction term is still present. This approach will identify the factors that independently alter the treatment effect and prevent identification of multiple correlated interactions.

Any quantitative interactions identified using this procedure will then be tested to rule out any qualitative interaction using the approach of Gail and Simon.[23]

The primary analysis of PFS will be based on the programmatically derived PFS based on an ICR of radiological data and using all scans regardless of whether they were scheduled or not. To assess the potential impact of informative censoring on the primary analysis of PFS, a sensitivity analysis using PFS derived from site assessments will be performed. Full details of the planned sensitivity analyses will be provided in the SAP.

The primary analysis will be performed on the FAS.

Patients whose data contributed to the Part 1 analysis will not contribute to the Part 2 analysis.

8.5.1.3 Part 2 – Overall Survival

In Part 2, the primary analysis will test for the superiority of varlitinib-containing treatment arm relative to the placebo-containing arm, as assessed by OS.

The primary analysis of OS will be performed after the 247th documented OS event. OS will be analyzed using the methods described in Section 8.5.1.2 for PFS.

Patients whose data contributed to the Part 1 analysis will not contribute to the Part 2 analysis.

8.5.2 Secondary Endpoints

8.5.2.1 Efficacy Endpoints

Progression-free survival based on site assessments

In all study parts, PFS based on the site review of radiological data is a secondary endpoint. PFS based on site data will be analyzed using the same model and methodology as described in Section 8.5.1.2 for PFS based on ICR.

Further details will be provided in the SAP.

Duration of Response

The DoR will not be formally analyzed. Duration of response will be listed and presented using KM curves. Descriptive statistics, based on the KM estimates, will be presented by treatment group.

Overall Survival (Part 1)

In Part 1, OS will be analyzed using the methods described in Section 8.5.1.2 for PFS. OS will be analyzed twice. The initial analysis of OS will be performed at the time of the primary analysis of ORR and PFS. Due to the number of OS events expected at the time of the first analysis, this initial analysis of OS will be considered exploratory only. Although a p-value may be presented, for the purpose of marketing authorization, no claims of statistical significance will be based on the initial analysis. A further OS update analysis is performed when approximately 95 OS events have occurred. To support marketing authorization, for the purpose of type I error control across the two analyses of OS, the OS update analysis will be considered the primary analysis of OS in the study.

Disease Control Rate

Disease control rate will be analyzed using a stratified exact binomial test[16] that extends Fisher's Exact test to more than 1 stratum. The analysis will be stratified by primary tumor location (GB/Non-GB). The 2-sided p-value will be obtained by doubling the 1-sided p-value.

The conditional maximum likelihood estimate of the odds ratio will be presented together with its exact 2-sided 95% confidence limit, which excludes one if and only if the stratified exact binomial test is significant a 2-sided 5% level. Corresponding significance levels and CIs will be calculated using tests performed at a 1-sided 10% level. The 1-sided p-value will also be presented.

To test for heterogeneity across strata, the exact test of Zelen will be performed testing whether the treatment effect differs between the 2 strata included in the primary analysis.

Tumor Size

The percentage change from baseline in tumor size at Week 12 ($\%\Delta TS_{Wk12}$) is a secondary endpoint for Part 1. Tumor size is not considered to be a key secondary endpoint; for the purpose of marketing authorization no statistical claims will be based on tumor size.

Tumor size will be presented graphically using waterfall plots for each treatment arm, presenting each patient's Week 12 percentage change in tumor size as a separate bar with the bars ordered from the largest increase to the largest decrease. Reference lines at the +20% and –30% change in tumor size levels will be added to the plots, which correspond with the definitions of disease progression and PR, respectively. In these waterfall plots, the patients whose Week 12 percentage change in tumor size is based on an imputation will be clearly shown. The 2 treatment arms will be plotted separately, but presented side-by-side on a single page.

Waterfall plots of the best percentage change from baseline will also be presented, as described above for the Week 12 percentage change from baseline.

Tumor size will also be used to help evaluate the exploratory objectives of exploring relationships between baseline biomarker levels and clinical outcomes (e.g., baseline HER2 status and clinical outcome, and other HER family statuses and clinical outcomes).

In line with the exploratory objectives of the study, the statistical analysis of tumor size in Part 1 will be also be used to help evaluate the role of HER family expression levels status as a predictor of benefit to varlitinib. If a relationship is found between biomarker(s) expression and clinical outcomes in Part 1 of the study, the biomarker(s) could be prospectively evaluated in Part 2 of the study.

These analyses will be exploratory, and may be driven by the data observed, and specifically the prevalence of the HER family sub-groups of interest. However, the analysis principles to be followed are outlined below.

1. ASLAN will create and document a list of the key biomarkers of interest, based upon the biological plausibility of predictivity for clinical outcomes. The list will be limited to those biomarkers, or combinations of biomarkers for which a scientific hypothesis exists. These will represent the biomarkers that will be used

to assess the listed exploratory objectives, providing that there is sufficient prevalence of that biomarker in the study population.
2. For each biomarker of interest, each patient's baseline biomarker status will be independently evaluated blinded to study treatment and clinical outcome
3. For each biomarker sub-group, or combination of biomarkers identified on the prospectively defined list (step 1), if at least 15 patients in the EFR population are determined to be expressors, then the role of that biomarker as a predictor of clinical outcome (tumor size) will be evaluated as described below.

For each biomarker of interest (or combination of biomarkers), the absolute values at baseline and Week 12, along with the percentage change from baseline target lesion size at Week 12 will be summarized using descriptive statistics and presented by treatment arm and baseline biomarker status.

The number and percentage of patients in each treatment arm whose Week 12 data is imputed will also be presented (split by biomarker sub-group).

The effect of varlitinib on percentage change in tumor size will be estimated from an analysis of covariance (ANCOVA) model fitting the Week 12 percentage change from baseline as the response variable, and treatment, primary tumor location (GB/Non-GB), baseline biomarker status (positive or negative), the interaction treatment x baseline biomarker status, baseline tumor size, and the time from the baseline scan to randomization as covariates.

The significance of the interaction term will be evaluated at the 1-sided 10% level to determine whether there is evidence of a treatment by biomarker interaction. Regardless of the significance of the interaction term, the number of patients, unadjusted mean and adjusted least squares (LS) means for each treatment arm will be presented for each level of biomarker status factor (positive or negative), together with the difference in adjusted LS means between treatment arms for each level of the biomarker status factor and corresponding p-value and 80% and 95% CIs for the difference.

If the interaction term is not significant at the 1-sided 10% level, the number of patients, unadjusted mean and adjusted least squares (LS) means for each treatment arm will also be presented together with the difference in adjusted LS means between treatment arms and corresponding p-value and 80% and 95% CIs for the difference.

If, at blind review, it is judged that the data do not adequately follow a normal distribution assumption, then a log-transformation may be used. Specifically in place of percent change in Week 12 value the ANCOVA model will use loge (Week 12/baseline). In this situation, the ratio of the geometric LS means corresponding CI and p-value will be presented.

As a sensitivity analysis, a nonparametric analysis will be performed. The Hodges Lehmann estimate of the median difference and corresponding 80% CI will be derived and presented. The median percentage change and range will be presented for each

treatment arm, together with the number of patients and percentage of patients in each treatment arm whose Week 12 data is imputed in the nonparametric analysis.

For all biomarkers of interest (step 1), waterfall plots color-coded by baseline biomarker status will be produced.

Note, due to the differing timeframes of the endpoints being available for analysis, the above statistical analyses of the biomarker data will be reported outside of the study CSR.

8.5.2.2 Safety Data Analysis

For each study part, safety data will be assessed for the safety population.

All AE data will be listed along with information regarding initial study dose, dose at onset, onset time (study day), duration, severity, and relationship to study treatment.

Treatment emergent AEs (TEAEs) are defined as AEs with an onset date on or after the start of treatment. The following summaries will be produced, by treatment group and overall for all TEAEs:

- An overview table of the incidence of TEAEs, grade 3+ TEAEs, SAEs, TEAEs leading to treatment discontinuation and TEAEs leading to death, by treatment arm and overall. For each summary category, the results will be shown overall (regardless of causality), and for the incidence of causally-related TEAEs. For example, the overall incidence of TEAEs will be presented, as well as the incidence of TEAEs related to randomized therapy, the incidence of TEAEs related to capecitabine and the incidence TEAEs related to both randomized therapy and capecitabine.

- Summary of TEAEs by system organ class and preferred term: Both the number and percentage of patients in each category (patient-level summary) and the number of episodes (episode-level summary). This summary table will be repeated for TEAEs attributed as *causally related to randomized therapy* (varlitinib or placebo)

- Summary of TEAEs occurring in at least 10% of patients, sorted in descending order of frequency (i.e., most frequent event shown first). The order of frequency will be determined by the most frequent preferred term across both arms, regardless of CTC grade. For each event, the results will be presented for all CTC grades, and also split by grade 1-2, and grade 3+.

- Summary of TEAEs attributed as *causally related to randomized therapy* occurring in at least 10% of patients, sorted in descending order of frequency (i.e., most frequent event shown first). The order of frequency will be determined by the most frequent preferred term across both arms. For each event, the results will be presented for all CTC grades, and also split by grade 1-2, and grade 3+.

- Summary of CTC grade 3 and above TEAEs sorted in descending order of frequency (i.e., most frequent event shown first). The order of frequency will be determined by the most frequent preferred term across both arms.

- A summary or CTC grade 3 and above TEAEs attributed as *causally related to randomized* therapy sorted in descending order of frequency (i.e., most frequent event shown first). The order of frequency will be determined by the most frequent preferred term across both arms.

- Summary of SAEs by preferred term

- Summary of SAEs attributed as *causally related to randomized* therapy, sorted by preferred term

- Categorical Analysis of ECG findings (See Section 8.5.2.3)

Additionally, the following will be listed:

- AEs with outcome of death along with the date of onset, dosing day, dose at onset, treatment status at onset (pre-treatment, ongoing or post-treatment) and Investigator's assessment of severity and relationship to study drug

- All SAEs along with the date of onset, dosing day, dose at onset, treatment status at onset (pre-treatment, ongoing or post-treatment), date of resolution (if AE is resolved), Investigator's assessment of severity and relationship to study drug

- AEs leading to discontinuation of study medication, listed along with the date of onset, dosing day, dose at onset, treatment status at onset (pre-treatment, ongoing or post-treatment) and Investigator's assessment of severity and relationship to study drug

If an AE is reported more than once during the study period, the greatest severity and the worst-case attribution will be presented in summary tables. Any AEs commencing > 28 days after discontinuation of study treatment will not be included in the tabulations of AE data.

All clinical laboratory data (clinical chemistry, hematology and urinalysis data), vital signs and ECG data will be listed. Data tabulations and graphical displays of clinical laboratory data (clinical chemistry, hematology, and urinalysis data), vital signs and ECG data, will include all assessments from screening up to (and including) 28 days after discontinuation of study treatment. In addition, all data measured on a continuous scale (except respiration rate and pulse) will be displayed graphically as described below:

Safety lead-in:

- Patient profile plots of laboratory data over time, including reference lines at the LLN and ULN. Any dose reductions will be indicated on the plots using a change in line-type.

- Patient profile plots of the change from baseline over time, including a horizontal reference line at zero. Any dose reductions will be indicated on the plots using a change in line-type.

Parts 1 and 2:

- Box plots of laboratory data over time, by treatment, including reference lines at the LLN and ULN

- Box plots of the change from baseline over time, by treatment, including a horizontal reference line at zero

To enable assessment of the potential for drug-induced liver injury, for all study parts the following outputs will be produced:

- A scatter plot of maximum on-treatment ALT versus maximum on-treatment total bilirubin (x-axis), both expressed as multiples of the upper limit of normal (ULN), including reference lines at 3×ULN for ALT, and 2×ULN for total bilirubin. For each patient, the maximum ALT and maximum total bilirubin may occur at different visits

- A scatter plot of maximum on-treatment AST versus maximum on-treatment total bilirubin (x-axis), both expressed as multiples of the upper limit of normal (ULN), including reference lines at 3 × ULN for AST, and 2 × ULN for total bilirubin. For each patient, the maximum AST and maximum total bilirubin may occur at different visits.

In the event that the scatter plots of ALT or AST against bilirubin identify any potential Hy's law cases (patients with either both ALT > 3 × ULN and total bilirubin > 2 × ULN, or both AST > 3 × ULN and total bilirubin > 2 × ULN), profile plots over time will be produced for these patient's liver function tests (ALT, AST, ALP, and total bilirubin), expressed in multiples of the ULN, showing all 4 LFT parameters on the same plot.

Physical examination data will be listed.

To further assess the tolerability of varlitinib, exposure and dose intensity will be listed and summarized by treatment arm. Further details will be provided in the study SAP.

8.5.2.3 ECG/QT Analysis

For the Safety lead-in, exploratory descriptive and categorical analyses, including change from baseline will be performed to investigate the impact of varlitinib and capecitabine treatments on the changes from baseline in ECG parameters.

For Part 1 of the study, a multi-step approach will be applied to evaluate the effect of capecitabine alone and varlitinib in combination with capecitabine on the ECG parameters at different time points post-dose. The comparisons will be done between ECG values at each time point post-dose and baseline and between treatment arms with and without varlitinib for each time point individually. The evaluation of the cardiodynamic effects of capecitabine and varlitinib may be explored using exposure-response modeling if there appears to be a meaningful effect of varlitinib when added to capecitabine on the ECG parameters including QTcF. This will be further described in the SAP.

Central Tendency Analysis will be performed for both the Safety lead-in and Part 1 of the study, the change from baseline in QTcF, PR, QRS, QTcB, and heart rate, will be summarized by time point (and treatment arm for Part 1) using descriptive statistics (n, mean, SD, min, median, max, 90% confidence intervals).

For both the Safety lead-in and Part 1, the following categorical data will be summarised:
- The proportion of patients obtaining treatment-emergent absolute QTcF values > 450 msec and ≤ 480 msec; > 480 msec and ≤ 500 msec; and > 500 msec
- The proportion of patients obtaining a QTcF increase from baseline values ≥ 30 and <60 msec and ≥ 60 msec
- The proportion of patients obtaining a QRS change from baseline > 25% resulting in QRS > 120 msec
- The proportion of patients obtaining a PR interval change from baseline >25% reaching a value >220 msec
- The proportion of patients obtaining a > 25% decrease from baseline in heart rate resulting in a heart rate < 50 beats per minute (bpm) or a > 25% increase from baseline in heart rate resulting in a heart rate > 100 bpm

For Part 1 of the study, the above categorical data summaries will be presented by treatment arm.

Following this, categorical analyses will be applied to the categorical data summaries above.

Additionally, T-wave morphology will be analyzed. The morphological T-wave analysis will be focusing on the change from baseline, i.e., treatment emergent changes.

Following Part 1 of the study, a formal statistical analysis will be performed to assess the potential impact of varlitinib and capecitabine on changes in the ECG parameters.

The statistical stepwise approach will be used to separate the cardiodynamic effect of varlitinib from normal circadian fluctuation in the ECG values and from the effect of capecitabine:

1. ANOVA mixed effects comparison of the absolute values of ECG parameters at each time point vs baseline using treatment as a fixed effect in order to evaluate the contribution of circadian fluctuation and

to determine how treatment differences contribute to the changes. The ECG parameter values will be log-transformed and the resulting output will include the geometric mean ratio for test vs reference with the corresponding confidence interval and p-value. Interaction term, time point x treatment, will be also evaluated if the data allow.

2. ANOVA comparison of the absolute values of ECG parameters as well as change from baseline (ΔECG) between treatments for each post-dose time point assessed separately in order to separate the varlitinib effect from that of capecitabine. The ECG parameter values will be log-transformed and the resulting output will include the geometric mean ratio for test vs reference with the corresponding confidence interval and p-value. ΔECG will be tested as untransformed and log-transformed parameters to avoid bias from discarding 0 ΔECG values from the comparisons.

3. Exposure-Response Analysis: Linear mixed effect model between ΔQTcF and time matched concentrations of varlitinib and other potential metabolites if measured and as appropriate. Other ECG variable may be similarly analyzed and other models used, if appropriate.
   3.1 ΔQTcF will be calculated as the difference between each time point value and the average baseline value for each arm with the combination varlitinib/capecitabine treatment.

   3.2 ΔΔQTcF will be calculated for each patient in the combination arm individually as the difference between the ΔQTcF value for the arm with combination varlitinib/capecitabine treatment and the average value of all patients in the capecitabine alone arm matching time point. Other ECG parameters may also be used in the analysis including QTcB, heart rate, etc to provide supporting information.

   3.3 Base linear mixed effect model will include patients as a random effect.

   3.4 The total dose of capecitabine may be included as a fixed effect in the model to account for differences in total doses received by subjects with different body surface area.

4. Linear mixed effect model between ΔQTcF parameters and time matched concentrations of capecitabine and 5-FU (metabolite of capecitabine) and other potential metabolites if measured and as appropriate

4.1. ΔQTcF will be calculated for all patients in both arms as the difference between each time point value and the average baseline value.

4.2. Base linear mixed effect model will include patients as a random effect and treatment (capecitabine alone or in combination with varlitinib) as a fixed effect; the total capecitabine dose may also be used as a fixed effect.

5. Different covariates may be included in the complex models in addition to the base model as fixed effects such as time point in order to ensure the model feasibility and to evaluate covariates influential to ECG parameters.

The results of the fitted models will be presented using statistical parameters such as the geometric mean ratios and corresponding confidence intervals (for ANOVA) and estimates of the slope, and associated confidence interval for the linear mixed effect models.

In addition, the following graphic exploration of the exposure-ECG relationship may be performed:

- Residual plots to predict results
- Double Y plots with time on the X axis and time matched values of PK concentrations for varlitinib and capecitabine on the Y1 axis, ΔECG on the Y2 axis to determine the possibility of hysteresis between drug concentration and cardiodynamic effects
- Regression/scatter plots with time matched concentrations of varlitinib and capecitabine on the X axis and ΔECG on the Y axis
- Regression/scatter plots with varlitinib or capecitabine non-compartmental PK parameters of C_{max}, C_{trough}, AUC_{tau} and others on the X axis and maximum ΔECG on the Y axis
- Forest plots for different categories in ECG changes vs mean (SD) non-compartmental PK parameters for varlitinib or capecitabine on the X axis

9 QUALITY ASSURANCE AND QUALITY CONTROL

9.1 Audit and Inspection

Study centers and study documentation may be patient to Quality Assurance audit during the course of the study by the sponsor or its nominated representative. In addition, inspections may be conducted by regulatory authorities at their discretion.

9.2 Monitoring

Data for each patient will be recorded on a CRF. Data collection must be completed for each patient who signs an ICF and is administered study drug.

In accordance with GCP and ICH guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the CRF are accurate and reliable.

The Investigator must permit the monitor, the IEC/IRB, the sponsor's internal auditors, and representatives from regulatory authorities direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the CRFs.

9.3 Data Management and Coding

The designated CRO will be responsible for activities associated with the data management of this study. This will include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical study will be handled according to the relevant standard operating procedures (SOPs) of the data management and biostatistics departments of sponsor or the designated CRO.

Study centers will enter data directly into an EDC system by completing the CRF via a secure internet connection. Data entered into the eCRF must be verifiable against source documents at the study center. Data to be recorded directly on the eCRF will be identified and the eCRF will be considered the source document. Any changes to the data entered into the EDC system will be recorded in the audit trail and will be FDA CFR 21 Part 11 compliant.

Medical coding will use Medical Dictionary for Regulatory Activities (MedDRA) for concomitant diseases and AEs and WHO Drug for medications.

Missing or inconsistent data will be queried in writing to the Investigator for clarification. Subsequent modifications to the database will be documented.

10 RECORDS AND SUPPLIES

10.1 Drug Accountability

On receipt of the study medication (varlitinib, placebo, and capecitabine), the Investigator (or deputy) will conduct an inventory check of the supplies and verify that study drug supplies are received intact and in the correct amounts as in the patient dosing diary, before completing a supplies receipt. The Investigator will retain a copy of this receipt at the study center and return the original receipt to the study monitor. The monitor may check the study supplies at each study center at any time during the study.

It is the responsibility of the study monitor to ensure that the Investigator (or deputy) has correctly documented the amount of the study drug received, dispensed, and returned on the dispensing log that will be provided. A full drug accountability log will be maintained at the study center at all times. The study monitor will arrange collection of unused study drug returned by the patient. The study monitor will also perform an inventory of study drug at the close-out visit to the study center. All discrepancies must be accounted for and documented.

10.2 Financing and Insurance

Financing and insurance of this study will be outlined in a separate agreement between the designated CRO and the sponsor.

11 ETHICS

11.1 Independent Ethics Committee or Institutional Review Board

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the patients, and any other relevant study documentation will be submitted to the appropriate IEC/IRB. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the study drug is released to the Investigator. Any necessary extensions or renewals of IEC/IRB approval must be obtained for changes to the study such as amendments to the protocol, the ICF or other study documentation. The written approval of the IEC/IRB together with the approved ICF must be filed in the study files.

The Investigator will report promptly to the IEC/IRB any new information that may adversely affect the safety of the patients or the conduct of the study. The Investigator will submit written summaries of the study status to the IEC/IRB as required. On completion of the study, the IEC/IRB will be notified that the study has ended.

11.2 Regulatory Authorities

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval

before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

11.3 Ethical Conduct of the Study

The Investigators and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines, and the applicable national and local laws and regulatory requirements.

Study ASLAN001-009 will be performed in compliance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice (ICH GCP) and local regulatory requirements. Aspects of the study concerned with the study medication will meet the requirements of Good Manufacturing Practice.

11.4 Informed Consent

The process of obtaining informed consent must be in accordance with applicable regulatory requirements and must adhere to GCP.

The Investigator is responsible for ensuring that no patient undergoes any study related examination or activity before that patient has given written informed consent to participate in the study.

The Investigator or designated personnel will inform the patient of the objectives, methods, anticipated benefits and potential risks and inconveniences of the study. The patient should be given every opportunity to ask for clarification of any points s/he does not understand and, if necessary, ask for more information. At the end of the interview, the patient will be given ample time to consider the study. Patients will be required to sign and date the ICF. After signatures are obtained, the ICF will be kept and archived by the Investigator in the Investigator's study file. A signed and dated copy of the patient ICF will be provided to the patient or their authorized representative.

Patients who agree to provide an optional tumor tissue sample (Section 7.1.4) will need to give written informed consent, in addition to consenting in the main part of the study.

It should be emphasized that the patient may refuse to enter the study or to withdraw from the study at any time, without consequences for their further care or penalty or loss of benefits to which the patient is otherwise entitled. Patients who refuse to give or who withdraw written informed consent should not be included or continue in the study.

If new information becomes available that may be relevant to the patient's willingness to continue participation in the study, a new ICF will be approved by the IECs/IRBs (and regulatory authorities, if required). The study patients will be informed about this new information and re-consent will be obtained.

11.5 Patient Confidentiality

Monitors, auditors, and other authorized agents of the sponsor and/or its designee, the IECs/IRBs approving this research, and the US FDA, as well as that of any other applicable agencies, will be granted direct access to the study patients' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the patients to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the patients' identity will remain confidential.

All personal data collected and processed for the purposes of this study should be managed by the Investigator and his/her staff with adequate precautions to ensure confidentiality of those data, and in accordance with the Health Insurance Portability and Accountability Act), applicable to national and/or local laws and regulations on personal data protection.

12 REPORTING AND PUBLICATION, INCLUDING ARCHIVING

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study (end of study defined as the date of the last visit of the last patient), all documents and data relating to the study, including digital ECGs, will be kept in an orderly manner by the Investigator in a secure study file. This file will be available for inspection by the sponsor or its representatives. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the study medication. It is the responsibility of the sponsor to inform the study center when these documents no longer need to be retained. The Investigator must contact the sponsor before destroying any study related documentation. In addition, all patient medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

The sponsor must review and approve any results of the study or abstracts for professional meetings prepared by the Investigator(s). Published data must not compromise the objectives of the study. Data from individual study centers in multicenter studies must not be published separately.

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14 APPENDICES

14.1 RECIST Criteria

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eur J Ca 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

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.

14.2 ECOG Performance Scale

Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed < 50% of the time. 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	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

14.3 Prohibited Concomitant Medication/Therapy

Category	Wash-out Period	Examples of prohibited concomitant medication *included but not limited to:
Strong CYP3A4 Inhibitors	21 days before first dose of study medication	Clarithromycin, Darunavir, Indinavir, Itraconazole, Ketoconazole, Lopinavir, Nefazodone, Nelfinavir, Ritonavir, Saquinavir, Telithromycin, Tipranavir, Grapefruit juice
Proton Pump Inhibitors	Not Applicable	Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole, Rabeprazole
H2 antagonist	Can only be taken 3 hours after investigational product	Cimetidine, Famotidine, Nizatidine, Ranitidine
Any other investigational Product/Device	14 days before first dose of study medication	
Anti-emetic drugs with QT prolongation effects	Safety Lead-In (Cycle 1 Day 1 to Cycle 2 Day 1) Part 1 (Cycle 1 Day 1 to Cycle 2 Day 1)	Metoclopramide, Dolasetron, Granisetron, Ondansetron

14.4 Use with Caution: Drugs Associated with Torsade de Pointes and QT Prolongation

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Amiodarone	Cordarone, Pacerone, Nexterone	Antiarrhythmic	Abnormal heart rhythm
Anagrelide	Agrylin, Xagrid	Phosphodiesterase 3 inhibitor	Thrombocythemia
Arsenic trioxide	Trisenox	Anticancer	Cancer (leukemia)
Astemizole (Removed from Market)	Hismanal	Antihistamine	Allergic rhinitis
Azithromycin	Zithromax, Zmax	Antibiotic	Bacterial infection
Bepridil (Removed from Market)	Vascor	Antianginal	Angina Pectoris (heart pain)
Chloroquine	Aralen	Antimalarial	Malaria
Chlorpromazine	Thorazine, Largactil, Megaphen	Antipsychotic / Antiemetic	Schizophrenia, nausea, many others
Cilostazol	Pletal	Phosphodiesterase 3 inhibitor	Intermittent claudication
Ciprofloxacin	Cipro, Cipro-XR, Neofloxin	Antibiotic	Bacterial infection
Cisapride (Removed from Market)	Propulsid	GI stimulant	Increase GI motility
Citalopram	Celexa, Cipramil	Antidepressant, SSRI	Depression
Clarithromycin	Biaxin, Prevpac	Antibiotic	Bacterial infection
Cocaine	Cocaine	Local anesthetic	Anesthesia (topical)
Disopyramide	Norpace	Antiarrhythmic	Abnormal heart rhythm
Dofetilide	Tikosyn	Antiarrhythmic	Abnormal heart rhythm
Domperidone	Motilium, Motillium, Motinorm Costi, Nomit	Antinausea	Nausea, vomiting
Donepezil	Aricept	Cholinesterase inhibitor	Dementia (Alzheimer's Disease)
Dronedarone	Multaq	Antiarrhythmic	Abnormal heart rhythm

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Droperidol	Inapsine, Droleptan, Dridol, Xomolix	Antipsychotic / Antiemetic	Anesthesia (adjunct), nausea
Erythromycin	E.E.S., Robimycin, EMycin, Erymax, Ery-Tab, Eryc Ranbaxy, Erypar, Eryped, Erythrocin Stearate Filmtab, Erythrocot, E-Base, Erythroped, Ilosone, MY-E, Pediamycin, Zineryt, Abboticin, Abboticin-ES, Erycin, PCE Dispertab, Stiemycine, Acnasol, Tiloryth	Antibiotic	Bacterial infection, increase GI motility
Escitalopram	Cipralex, Lexapro, Nexito, Anxiset-E (India), Exodus (Brazil), Esto (Israel), Seroplex, Elicea, Lexamil, Lexam, Entact (Greece), Losita (Bangladesh), Reposil (Chile), Animaxen (Colombia), Esitalo (Australia), Lexamil (South Africa)	Antidepressant, SSRI	Depression (major), anxiety disorders

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Flecainide	Tambocor, Almarytm, Apocard, Ecrinal, Flécaine	Antiarrhythmic	Abnormal heart rhythm
Fluconazole	Diflucan, Trican	Antifungal	Fungal infection
Gatifloxacin (Removed from Market)	Tequin	Antibiotic	Bacterial infection
Grepafloxacin (Removed from Market)	Raxar	Antibiotic	Bacterial infection
Halofantrine	Halfan	Antimalarial	Malaria
Haloperidol	Haldol (US & UK), Aloperidin, Bioperidolo, Brotopon, Dozic, Duraperidol (Germany), Einalon S, Eukystol, Halosten, Keselan, Linton, Peluces, Serenace, Serenase, Sigaperidol	Antipsychotic	Schizophrenia, agitation
Ibogaine (Only on Non US Market)	None	Psychedelic	Narcotic addiction, unproven
Ibutilide	Corvert	Antiarrhythmic	Abnormal heart rhythm
Levofloxacin	Levaquin, Tavanic	Antibiotic	Bacterial infection
Levomepromazine (Only on Non US Market)	Nosinan, Nozinan, Levoprome	Antipsychotic	Schizophrenia
Levomethadyl acetate (Removed from Market)	Orlaam	Opioid agonist	Narcotic dependence

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Levosulpiride (Only on Non US Market)	Lesuride, Levazeo, Enliva (with rabeprazole)	Antipsychotic	Schizophrenia
Mesoridazine (Removed from Market)	Serentil	Antipsychotic	Schizophrenia
Methadone	Dolophine, Symoron, Amidone, Methadose, Physeptone, Heptadon	Opioid agonist	Narcotic dependence, pain
Moxifloxacin	Avelox, Avalox, Avelon	Antibiotic	Bacterial infection
Ondansetron	Zofran, Anset, Ondemet, Zuplenz, Emetron, Ondavell, Emeset, Ondisolv, Setronax	Antiemetic	Nausea, vomiting
Oxaliplatin	Eloxatin	Antineoplastic Agent	Cancer
Papaverine HCl (Intra-coronary)	none	Vasodilator, Coronary	Diagnostic adjunct
Pentamidine	Pentam	Antifungal	Fungal infection (Pneumocystis pneumonia)
Pimozide	Orap	Antipsychotic	Tourette's Disorder
Probucol (Removed from Market)	Lorelco	Antilipemic	Hypercholesterolemia
Procainamide	Pronestyl, Procan	Antiarrhythmic	Abnormal heart rhythm
Propofol	Diprivan, Propoven	Anesthetic, general	Anesthesia
Quinidine	Quinaglute, Duraquin, Quinact, Quinidex, Cin-Quin, Quinora	Antiarrhythmic	Abnormal heart rhythm

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Roxithromycin (Only on Non US Market)	Rulide, Xthrocin, Roxl-150, Roxo, Surlid, Biaxsig, Roxar, Roximycinv, Roxomycin, Rulid, Tirabicin, Coroxin	Antibiotic	Bacterial infection
Sevoflurane	Ulane, Sojourn	Anesthetic, general	Anesthesia
Sotalol	Betapace, Sotalex, Sotacor	Antiarrhythmic	Abnormal heart rhythm
Sparfloxacin (Removed from Market)	Zagam	Antibiotic	Bacterial infection
Sulpiride (Only on Non US Market)	Dogmatil, Dolmatil, Eglonyl, Espiride, Modal, Sulpor	Antipsychotic, atypical	Schizophrenia
Sultopride (Only on Non US Market)	Barnetil, Barnotil, Topral	Antipsychotic, atypical	Schizophrenia
Terfenadine (Removed from Market)	Seldane	Antihistamine	Allergic rhinitis
Terlipressin (Only on Non US Market)	Teripress, Glypressin, Terlipin, Remestyp, Tresil, Teriss and others	Vasoconstrictor	Septic shock
Terodiline (Only on Non US Market)	Micturin, Mictrol (not bethanechol)	Muscle relaxant	Bladder spasm
Thioridazine	Mellaril, Novoridazine, Thioril	Antipsychotic	Schizophrenia
Vandetanib	Caprelsa	Anticancer	Cancer (thyroid)

14.5 Drugs that Prolong the QTc and are Not Clearly Associated with Torsade de Pointes

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Alfuzosin	Uroxatral	Alpha1-blocker	Benign prostatic hyperplasia
Apomorphine	Apokyn, Ixense, Spontane, Uprima	Dopamine agonist	Parkinson's disease
Aripiprazole	Abilify, Aripiprex	Antipsychotic, atypical	Schizophrenia, depression (adjunct)
Artenimol+piperaquine	Eurartesim	Antimalarial	Malaria
Asenapine	Saphris, Sycrest	Antipsychotic, atypical	Schizophrenia
Atomoxetine	Strattera	Norepinephrine reuptake inhibitor	ADHD
Bedaquiline	Sirturo	Antibiotic	Tuberculosis, Multi-drug resistant
Buprenorphine	Butrans, Belbuca, Bunavail, Buprenex, Suboxone, Zubsolv	Opioid receptor modulator	Narcotic addiction and pain
Clomipramine	Anafranil	Antidepressant, Tricyclic	Depression
Clozapine	Clozaril, Fazaclo, Versacloz	Antipsychotic, atypical	Schizophrenia
Cyamemazine (cyamepromazine) (Only on Non US Market)	Tercian	Antipsychotic	Schizophrenia, sedation
Delamanid (Only on Non US Market)	Deltyba	Antibiotic	Tuberculosis, drug resistant
Desipramine	Pertofrane, Norpramine	Antidepressant, Tricyclic	Depression
Dexmedetomidine	Precedex, Dexdor, Dexdomitor	Sedative	Sedation
Dolasetron	Anzemet	Antiemetic	Nausea, vomiting
Efavirenz	Sustiva and others	Antiretroviral	HIV
Ezogabine (Retigabine)	Potiga, Trobalt	Anticonvulsant	Seizures, Partial
Famotidine	Pepcid, Fluxid, Quamatel	H2-receptor antagonist	Gastric hyperacidity, GERD
Felbamate	Felbatol	Anticonvulsant	Epilepsy
Fingolimod	Gilenya	Sphingosine phospate receptor modulator	Multiple Sclerosis

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Flupentixol (Only on Non US Market)	Depixol, Fluanxol	Dopamine 2 and 5HT2a antagonist	Schizophrenia
Foscarnet	Foscavir	Antiviral	Viral infection (HIV/AIDS)
Gemifloxacin	Factive	Antibiotic	Bacterial infection
Granisetron	Kytril, Sancuso, Granisol	Antiemetic	Nausea, vomiting
Hydrocodone - ER	Hysingla™ ER, Zohydro ER	Analgesic	Pain, severe
Iloperidone	Fanapt, Fanapta, Zomaril	Antipsychotic, atypical	Schizophrenia
Imipramine (melipramine)	Tofranil	Antidepressant, Tricyclic	Depression
Isradipine	Dynacirc	Antihypertensive	Hypertension
Lithium	Eskalith, Lithobid	Antimania	Bipolar disorder
Melperone (Only on Non US Market)	Bunil, Buronil, Eunerpan	Antipsychotic, atypical	Schizophrenia
Mifepristone	Korlym, Mifeprex	Progesterone antagonist	Pregnancy termination
Mirabegron	Myrbetriq	Beta3 adrenergic antagonist	Bladder spasm
Mirtazapine	Remeron	Antidepressant, Tetracyclic	Depression
Moexipril/HCTZ	Uniretic, Univasc	Antihypertensive	Hypertension
Nicardipine	Cardene	Antihypertensive	Hypertension
Norfloxacin	Noroxin, Ambigram	Antibiotic	Bacterial infection
Nortriptyline	Pamelor, Sensoval, Aventyl, Norpress, Allegron, Noritren, Nortrilen	Antidepressant, Tricyclic	Depression
Ofloxacin	Floxin	Antibiotic	Bacterial infection
Paliperidone	Invega, Xepilon	Antipsychotic, atypical	Schizophrenia
Pasireotide	Signifor	Somatostatin analog	Cushings Disease
Perphenazine	Trilafon, Etrafon/Triavil, Decentan	Antipsychotic	Schizophrenia
Pilsicainide (Only on Non US Market)	Sunrythm	Anti-arrhythmic	Arrhythmia

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Pipamperone (Only on Non US Market)	Dipiperon (E.U), Propitan (Japan), Dipiperal, Piperonil, Piperonyl	Antipsychotic	Schizophrenia
Promethazine	Phenergan	Antipsychotic / Antiemetic	Nausea, vomiting
Prothipendyl (Only on Non US Market)	Dominal, Largophren, Timoval, Timovan, Tumovan	Antipsychotic	Schizophrenia
Rilpivirine	Edurant, Complera, Eviplera	Antiviral	Viral infection (HIV/AIDS)
Risperidone	Risperdal	Antipsychotic, atypical	Schizophrenia
Saquinavir	Invirase(combo)	Antiviral	Viral infection (HIV/AIDS)
Sertindole (Only on Non US Market)	Serdolect, Serlect	Antipsychotic, atypical	Schizophrenia, anxiety
Solifenacin	VESIcare	Muscle relaxant	Bladder spasm
Tacrolimus	Prograf, Prograf, Advagraf, Protopic	Immunosuppressant	Immune suppression
Telavancin	Vibativ	Antibiotic	Bacterial infection
Telithromycin	Ketek	Antibiotic	Bacterial infection
Tetrabenazine	Nitoman, Xenazine	Monoamine Transporter Inhibitor	Chorea (Huntington's disease)
Tiapride (Only on Non US Market)	Tiapridal, Italprid, Sereprile, Tialaread, Tiaryl, Tiaprim, Tiaprizal, Sereprid, Tiapridex	Selective D2, D3 dopamine antagonist	Alcoholism, withdrawal
Tizanidine	Zanaflex, Sirdalud	Muscle relaxant	Muscle spasticity
Tolterodine	Detrol, Detrusitol	Muscle relaxant	Bladder spasm
Trimipramine	Surmontil, Rhotrimine, Stangyl	Antidepressant, Tricyclic	Depression
Tropisetron (Only on Non US Market)	Navoban, Setrovel	Antiemetic	Nausea, vomiting
Venlafaxine	Effexor, Efexor	Antidepressant, SNRI	Depression
Zotepine (Only on Non US Market)	Losizopilon, Lodopin, Setous and Zoleptil	Antipsychotic, atypical	Schizophrenia

14.6 Protocol Approval Signatures

Abbreviated Protocol Title:	Treatment Opportunity with Varlitinib in Biliary Tract Cancer (TreeTopp)
Protocol Title:	A multicenter, double-blind, randomized, placebo-controlled study of varlitinib plus capecitabine versus placebo plus capecitabine in patients with advanced or metastatic biliary tract cancer as second-line systemic therapy
Protocol Number:	ASLAN001-009
Protocol Version Number and Date:	Version 6.0, 13 Aug 2019

This study will be conducted in compliance with the clinical study protocol (and amendments), the International Council on Harmonisation (ICH) guidelines for current Good Clinical Practice (GCP), and applicable regulatory requirements.

Sponsor Signatory

[redacted]
Head of R&D
ASLAN Pharmaceuticals Pte. Ltd.

[redacted]
Signature

[redacted]
Date

[redacted]
Acting CMO
ASLAN Pharmaceuticals Pte. Ltd.

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Signature

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Date

14.7 Investigator Signature Page

Abbreviated Protocol Title:	Treatment Opportunity with Varlitinib in Biliary Tract Cancer (TreeTopp)
Protocol Title:	A multicenter, double-blind, randomized, placebo-controlled study of varlitinib plus capecitabine versus placebo plus capecitabine in patients with advanced or metastatic biliary tract cancer as second-line systemic therapy
Protocol Number:	ASLAN001-009
Protocol Version Number and Date:	Version 6.0, 13 Aug 2019

Confidentiality and GCP Compliance Statement

I, the undersigned, have reviewed this protocol (and amendments), including appendices, and I will conduct the study as described in compliance with this protocol (and amendments), GCP, and relevant ICH guidelines.

Once the protocol has been approved by the IEC/IRB, I will not modify this protocol without obtaining prior approval of ASLAN and of the IEC/IRB. I will submit the protocol amendments and/or any ICF modifications to ASLAN and IEC/IRB, and approval will be obtained before any amendments are implemented.

I understand that all information obtained during the conduct of the study with regard to the patients' state of health will be regarded as confidential. No patients' names will be disclosed. All patients will be identified by assigned numbers on all CRFs, laboratory samples, or source documents forwarded to the sponsor. Clinical information may be reviewed by the sponsor or its agents or regulatory agencies. Agreement must be obtained from the patient before disclosure of patient information to a third party.

Information developed in this clinical study may be disclosed by ASLAN Pharmaceuticals Pte. Ltd., to other clinical Investigators, regulatory agencies, or other health authority or government agencies as required.

_____ _____

Investigator Signature Date

_____

Printed Name

_____

Institution

14.8 Study Personnel

14.8.1 Sponsor Personnel

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