# CLINICAL STUDY PROTOCOL

## DZB-CS-301

## Derazantinib

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| **Study title:** | A pivotal study of derazantinib in patients with inoperable or advanced intrahepatic cholangiocarcinoma and *FGFR2* gene fusions or *FGFR2* gene mutations or amplifications |
| **Study number:** | DZB-CS-301 (formerly ARQ 087-301) |
| **Study phase:** | 2 |
| **Product name:** | Derazantinib (formerly ARQ 087) |
| **IND number:** | 116397 |
| **EudraCT number:** | 2016-004448-12 |
| **Sponsor:** | Basilea Pharmaceutica International Ltd.<br>Grenzacherstrasse 487<br>CH-4058 Basel<br>Switzerland |
| **Study Physician:** | [redacted] |
| **Version / Date:** | Protocol Version 9.0 / 17 November 2020 |



Note: This is an electronically controlled document (Document ID: Clinical-002427).

# SYNOPSIS

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| **Study title:** | A pivotal study of derazantinib in patients with inoperable or advanced intrahepatic cholangiocarcinoma and *FGFR2* gene fusions or *FGFR2* gene mutations or amplifications (FIDES-01) |
| **IND number:** | 116397 |
| **EudraCT number:** | 2016-004448-12 |
| **Study number:** | DZB-CS-301 |
| **Study Phase:** | Phase 2 |
| **Investigational product:** | Derazantinib |
| **Active ingredient:** | (R)-6-(2-fluorophenyl)-N-(3-(2-((2-methoxyethyl)amino)ethyl)phenyl) -5,6-dihydrobenzo[h]quinazolin-2-amine dihydrochloride |
| **Investigational device to screen for *FGFR2* fusions (Substudy 1):** | The *FGFR2* break-apart FISH Probe Kit test will be used to detect gene fusions, also referred to as rearrangements, involving the *FGFR2* gene via fluorescence *in situ* hybridization (FISH) in formalin-fixed paraffin-embedded (FFPE) primary liver cancer specimens, including intrahepatic cholangiocarcinoma (iCCA) tissue samples to aid in identifying or confirming patients' eligibility for treatment with derazantinib.<br>Tissue samples will be sent to ARUP laboratories, which is the Sponsor`s central laboratory, for FISH testing. Tumor samples may be analyzed at other laboratories identified by the Sponsor to further characterize the identified genetic aberrations (GAs) and molecular markers predictive of response.<br>Pre-screening results obtained from tests performed by the study sites ('local testing') detailed in Section 6.8 may enable treatment initiation prior to central confirmation of *FGFR2* fusions. |
| **Investigational device to screen for *FGFR2* mutations or amplifications (Substudy 2):** | For Next-Generation Sequencing (NGS) testing to detect *FGFR2* mutations/amplifications, no mandatory central laboratory will be established (see Section 6.8.2 for further details).<br>NGS testing will be performed or commissioned by the respective study site using standard protocols approved by the local Institutional Review Board (IRB) / Independent Ethics Committee (IEC), Clinical Laboratory Improvement Amendments (CLIA), or other similar agency, or, as applicable, US FDA-approved and/or fully CE-marked industrial-scale assays. For enrollment of patients in the EU, assays must be either fully CE-marked or CE-marked for analytical performance, |

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| | unless assays are exempt from this requirement by the In Vitro Diagnostics Directive (IVDD; *Directive 98/79/EC*), i.e., manufactured and appropriately validated within health-institution laboratories for use in that environment and not subject to commercial transactions. The use of both tissue- and plasma-based NGS assays is allowed.<br>Tumor samples may be analyzed at other laboratories identified by the Sponsor to further characterize the identified GAs and molecular markers predictive of response. |
| **Indication under investigation:** | **Substudy 1:**<br>Inoperable* or advanced *FGFR2* fusion positive iCCA.<br>**Substudy 2:**<br>Inoperable or advanced iCCA harboring *FGFR2* mutations or amplifications (see Appendix 8). |
| **Primary objective:** | **Substudy 1:**<br>To evaluate the anti-cancer activity by Objective Response Rate (ORR) by central radiology review as per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 in patients with inoperable or advanced iCCA whose tumors harbor *FGFR2* fusions (by FISH performed by a central laboratory) and who received at least one prior regimen of systemic therapy.<br>**Substudy 2:**<br>To evaluate the anti-tumor activity of derazantinib by progression-free survival at 3 months (PFS 3) based on survival status or central radiology review (RECIST 1.1) in patients with inoperable or advanced iCCA whose tumors harbor *FGFR2* mutations or amplifications, and who received at least one prior regimen of systemic therapy. |
| **Secondary objectives:** | **Substudy 1 and Substudy 2**<br>• To evaluate progression free survival (PFS) by central radiology review and overall survival (OS)<br>• To evaluate duration of response (DoR) by central radiology review<br>• To evaluate the safety profile (toxicities) of derazantinib in this patient population<br>• To evaluate changes, and assess the minimally important difference, in health-related quality-of-life (HRQOL) and symptom response from baseline using the European Organization for Research and Treatment of Cancer (EORTC) |

* Throughout this protocol, 'inoperable' means that surgery is not indicated due to disease extension, co-morbidities, or other technical reasons.

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| | QLQ-C30, QLQ-BIL21, Global- Self Evaluated Transition (G-SET) / Health Transition Index (HTI), and the EQ-5D visual analog scale (VAS).<br>**Substudy 2**<br>• To evaluate the anti-cancer activity by ORR by central radiology review as per RECIST version 1.1 in patients with inoperable or advanced iCCA whose tumors harbor *FGFR2* mutations or amplifications, and who received at least one prior regimen of systemic therapy |
| **Exploratory objectives:** | • To evaluate changes in pharmacodynamic (PD) biomarkers<br>• To evaluate ORR, PFS, OS, and DoR by PD biomarkers<br>• To evaluate the relationship between derazantinib exposure and effectiveness, toxicity and PD biomarkers<br>• To explore the concordance of a liquid biopsy diagnostic test compared to baseline tumor biopsy<br>• To evaluate population pharmacokinetics (PopPK)<br>• To evaluate the urinary excretion of derazantinib, and possibly its metabolites, in a subset of patients<br>• To compare time to progression (TTP) on the first and/or the last prior line of systemic therapy (reported) versus TTP on derazantinib by central radiology review (TTP will be calculated from the first date of receiving study drug or prior line of systemic therapy until radiographic disease progression) |
| **Study design:** | This is a multi-center, open-label, single arm study evaluating derazantinib in adult patients with inoperable or advanced iCCA and *FGFR2* GAs.<br>• **Substudy 1** enrolls patients with *FGFR2* fusions.<br>• **Substudy 2** enrolls patients with *FGFR2* mutations or amplifications (see Appendix 8).<br>• A subset of up to 20 patients (PK subgroup) will be asked to participate in rich PK blood sampling and PK urine sampling to assess the renal excretion of derazantinib (and its metabolites) (see Section 6.6).<br>Substudy 1 is considered pivotal, and will enroll approximately 100 patients to determine the ORR (see Section 10.7). |

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| | Substudy 2 will use a Simon's two-stage design, with approximately 15 mITT-evaluable patients in Stage 1, and an additional 28 mITT-evaluable patients if the study proceeds to Stage 2.<br><br>Patient eligibility may be assessed in two steps:<br><br>1) Molecular pre-screening to confirm *FGFR2* GA status (*FGFR2* fusions, or *FGFR2* mutations/amplifications; see Table 1 and Table 2, and Appendix 8) using validated/approved genetic testing devices; and<br><br>2) Clinical screening procedures to confirm study treatment eligibility once molecular eligibility is confirmed by the tumor's *FGFR2* GA status.<br><br>Molecular pre-screening for *FGFR2* fusions in Substudy 1 may be based on local or central testing. If pre-screening is performed based on a local test, then a central confirmation by the *FGFR2* break-apart FISH Probe Kit test is required for Substudy 1 (*FGFR2* fusions).<br><br>Molecular pre-screening for *FGFR2* mutations/amplifications in Substudy 2 should be based on NGS testing (for details, see Table 2 and Appendix 8) performed or commissioned by the respective study site.<br><br>Patients may be prescreened for the tumor's *FGFR2* GA status (prior to initiation of or during ongoing systemic therapy). If the patient is still receiving prior systemic therapy, clinical screening procedures will be delayed until radiographically confirmed disease progression or intolerance to the ongoing systemic therapy is documented. After the study treatment eligibility is confirmed, patients will be enrolled and treated with continuous 300 mg once daily (QD) dosing of derazantinib capsules. A treatment cycle is defined as 28 days.<br><br>During the treatment period, patients will be evaluated every 2 weeks for the first cycle (Cycle 1 Days 1 and 15) and once every cycle thereafter (Day 1 of each cycle).<br><br>Tumor measurements will be done at Screening (within 28 days prior to the first dose of derazantinib), once every 8 weeks (two cycles) from the day of the first dose for the first six cycles, and once every 12 weeks (three cycles) thereafter. For patients with partial response (PR) or complete response (CR), the Investigator should perform a confirmation tumor measurement 4 to 5 weeks after the scan showing PR or CR. For patients with progressive disease (PD) per Investigator assessment, a central |

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| | radiology reviewer confirmation should be received prior to the patient's discontinuation from the study treatment if progression is seen on the first or second on-treatment scan. Patients who discontinue study drug for a reason other than radiographic disease progression, withdrawal of consent, death, or loss to follow-up should continue tumor evaluation visits if possible every 8–12 weeks until they start another anti-cancer therapy, experience disease progression, withdraw consent, die, or are lost to follow-up.<br><br>Pharmacodynamic assessment will include evaluation of tumor markers (CA19.9, CA125, CEA), biomarkers (FGF19, FGF21, FGF23), and cell-free circulating tumor deoxyribonucleic acid (ctDNA). Blood samples for PD assessments will be collected only from patients enrolled after completion of the interim analysis, and subject to the granting of appropriate regulatory and IRB/IEC approval.<br><br>Archival tumor tissue samples will be obtained for all patients to enable additional molecular analyses with regard to the identified GAs and markers predictive of response at the laboratories selected by the Sponsor (see Section 6.8).<br><br>The PopPK parameters of derazantinib will be determined. Exploratory assessments of metabolites of derazantinib may also be investigated. All patients will be scheduled for sparse PK sampling. A subset of up to 20 patients (PK subgroup) will be asked to participate in rich PK sampling and/or urinary PK sampling (see Section 6.6).<br><br>HRQOL and symptom response will also be measured.<br><br>Safety follow-up will be conducted at least 30 days after the administration of the last dose of study medication. Safety follow-up will include collection of adverse events (AEs) and changes in concomitant medication.<br><br>Central reading of all electrocardiogram (ECG) results will be performed (for details, see Section 6.4).<br><br>Survival follow-up will continue until the study has completed or other discontinuation criteria are met. |
| **Study endpoints** | <u>Primary efficacy endpoint (Substudy 1)</u><br>• ORR will be the proportion of patients with confirmed complete responses and partial responses by central radiology review as per RECIST version 1.1. |

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| | <u>Primary efficacy endpoint (Substudy 2)</u><br>• PFS 3 will be the proportion of patients who have progression-free survival at 3 months from the first date of receiving study drug as assessed by survival status and central radiology review as per RECIST version 1.1.<br><u>Secondary efficacy endpoints (Substudy 1 and Substudy 2)</u><br>• DoR will be calculated from the first date of documented tumor response to disease progression by central radiology review.<br>• PFS will be calculated from the first date of receiving study drug until radiographic disease progression by central radiology review or death.<br>• OS will be calculated from the first date of receiving study drug until death.<br>• Changes in HRQOL and symptom response will be evaluated using the EORTC QLQ-C30, QLQ-BIL21, and EQ-5D VAS.<br><u>Secondary efficacy endpoint (Substudy 2)</u><br>• ORR will be the proportion of patients with confirmed complete responses and partial responses by central radiology review as per RECIST version 1.1.<br><u>Exploratory efficacy endpoints</u><br>• Changes in tumor markers and biomarkers from baseline to maximum change during the course of the treatment will be evaluated.<br>• ORR, PFS, OS, and DoR will be evaluated by molecular profile, gene expression profile, biomarkers.<br>• Describe the proportion of patients with concordant molecular assessment from a liquid biopsy sample measuring GAs in circulating-cell free DNA compared to the DNA obtained at from a tumor biopsy at baseline.<br>• TTP will be calculated based on central radiology review from the first date of receiving study drug or prior line of systemic therapy until radiographic disease progression).<br>– TTP will be evaluated for derazantinib overall and by line of prior systemic therapy.<br>– In addition, TTP will be assessed on the first and/or the last prior line of systemic therapy (reported) and will be compared to TTP on derazantinib |

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| | • PopPK parameters of derazantinib will be evaluated (in addition, exploratory assessments of metabolites of derazantinib may also be investigated from the plasma PK samples).<br>• The percentage of administered derazantinib (and possibly its metabolites) in urinary excretion over 24 h at steady-state may also be investigated.<br>• The exposure-response relationship between derazantinib exposure and study measures of efficacy, toxicity and PD biomarkers will be analyzed.<br><u>Safety endpoint</u><br>Toxicities will be evaluated using NCI CTCAE version 4.03 criteria. |
| **Study duration:** | Approximately 4 years |
| **Sites and location:** | Up to approximately 70 sites in the USA, Canada, Europe, Asia, and Latin America |
| **Planned sample size:** | This is a single-arm, open-label study with group-sequential design.<br>**Substudy 1 (iCCA with *FGFR2* fusions)**<br>Approximately 100 patients who meet the study entry criteria will receive 300 mg QD orally of derazantinib capsules. In order to evaluate 100 patients for efficacy, it is anticipated that over 1,000 patients will be tested for the presence of an *FGFR2* fusion.<br>**Substudy 2 (iCCA with *FGFR2* mutations or amplifications)**<br>Up to approximately 43 mITT-evaluable patients who meet the study entry criteria will receive 300 mg QD orally of derazantinib capsules.<br>A Simon's two-stage design will be used, with 15 mITT-evaluable patients in Stage 1, and an additional 28 mITT-evaluable patients if the study proceeds to Stage 2.<br>In order to evaluate 43 patients for efficacy, it is anticipated that more than 800 patients will be tested for the presence of *FGFR2* mutations or amplifications. |
| **Study population:** | The study population consists of patients with inoperable or advanced iCCA and with *FGFR2* fusions (Substudy 1) or *FGFR2* mutations/amplifications (Substudy 2), treated with at least one prior regimen of systemic therapy. |

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| | Patients' eligibility may be assessed in two steps: 1) pre-screening to assess the *FGFR2* GA status, which will be followed by 2) clinical screening procedures.<br>Tissue samples for genetic testing will be obtained from patients who meet the following pre-screening eligibility criteria:<br>1. Signed written informed consent to permit tissue analysis<br>2. 18 years of age or older<br>3. No medical history that is excluded per the study treatment eligibility criteria<br>4. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 (Appendix 2)<br>5. Eligible for or receiving systemic therapy for inoperable or advanced iCCA<br>6. Not currently eligible for curative local or surgical therapy<br>To be enrolled in the study, once the *FGFR2* GA status is determined, each prospective patient must meet all of the following inclusion criteria and none of the exclusion criteria.<br><u>Inclusion criteria</u><br>1. Signed written informed consent granted prior to initiation of any study-specific procedures<br>2. 18 years of age or older<br>3. Histologically or cytologically confirmed locally advanced, inoperable (where surgery is not indicated due to disease extension, co-morbidities, or other technical reasons), or metastatic iCCA or mixed histology tumors (combined hepatocellular-cholangiocarcinoma [cHCC-CCA])<br>4. **Substudy 1**:<br>*FGFR2* fusion status based on the following assessments:<br>a) If central laboratory designated by the Sponsor: Positive FISH test; and/or<br>b) If non-central laboratory:*<br>i) Positive FISH or NGS test: patients may be enrolled and may start dosing, but central confirmation is required** (see Section 5.7.1)<br>* Using standard protocols and approved by local IRB/IEC, CLIA, or other similar agency. For enrollment of patients in the EU, assays must be fully CE-marked.<br>** The patient must not be enrolled if a negative FISH test is obtained from the central laboratory prior to commencing study treatment. Patients without central confirmation of an *FGFR2* fusion by the central FISH test will be assessed on a case-by-case basis (see Section 5.7.1). |

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| | ii) Negative FISH or NGS test: tissue may be submitted to the central laboratory designated by the Sponsor, and patients may only be enrolled if the central test is positive<br><br>**Substudy 2**:<br>*FGFR2* mutations/amplifications without any concurrent *FGFR2* translocations based on NGS testing performed or commissioned by the respective study site (see Section 6.8.2 for further details). .<br><br>*Note 1: If the FGFR2 mutation/amplification status is derived from plasma-based NGS testing, a tumor block or slides prepared thereof should be submitted for subsequent correlative tissue-based NGS test at a laboratory identified by the Sponsor.*<br><br>*Note 2: If the NGS test used cannot identify FGFR2 translocations, a FISH test is mandatory to confirm that none are present.*<br>5. Received at least one regimen of prior systemic therapy and then experienced documented radiographic progression (for Substudy 1), and have no satisfactory treatment alternatives (for Substudy 2)<br>6. Measurable disease by RECIST version 1.1 criteria<br>7. ECOG performance status ≤ 1 (Appendix 2)<br>8. Adequate organ functions as indicated by the following laboratory values (based on screening visit values from the central laboratory).<br>• Hematological<br>– Hemoglobin (Hgb) ≥ 9.0 g/dL<br>– Absolute neutrophil count (ANC) ≥ $1.5 \times 10^9$/L<br>– Platelet count ≥ $75 \times 10^9$/L<br>– International normalized ratio (INR) 0.8 to upper limit of normal (ULN) or ≤ 3 for patients receiving anticoagulant therapy such as warfarin or heparin<br>• Hepatic<br>– Total bilirubin ≤ 2 × ULN<br>– Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 ULN (≤ 5 × ULN for patients with liver metastases)<br>– Albumin ≥ 2.8 g/dL<br>• Renal<br>– Serum creatinine ≤ 1.5 × ULN, or<br>– Creatinine clearance of ≥ 30 mL/min as estimated by the Cockcroft-Gault equation |

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| | 9. Female and male patients of child-producing potential must agree to avoid becoming pregnant or impregnating a partner, respectively, during the study*, and for at least 120 days after the last dose of derazantinib.<br><br>Male patients are considered not to be of child-producing potential if they have azoospermia (whether due to vasectomy or an underlying medical condition). Female patients are considered not to be of child-producing potential if they are:<br>• postmenopausal†, or<br>• have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening, or<br>• have a congenital or acquired condition that prevents childbearing.<br><br>Male or female patients of child-producing potential must agree to comply with one of the following until at least 120 days after the last dose of derazantinib:<br>a) Abstinence from heterosexual activity‡<br>b) Using (or having their partner use) a highly effective method of contraception during heterosexual activity. Highly effective methods of contraception are§:<br>• an intrauterine device (IUD)<br>• vasectomy of a female patient's male partner<br>• a contraceptive rod implanted into the skin<br>• combined (estrogen- and progestogen-containing) or progestogen-only hormonal contraception associated with inhibition of ovulation (oral contraceptive pill [estrogen/progestin pill or progestin-only pill] contraceptive skin patch/implant, vaginal contraceptive ring, or subcutaneous contraceptive injection) |

* From the day of first study medication, or for oral contraception from 14 days before first study medication.

† Postmenopausal is defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post -menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is not sufficient.

‡ Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if it is employed during the entire period of risk associated with the study treatment and if it is considered highly effective by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not highly effective methods of contraception.

§ If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as a highly effecive method of contraception for subjects participating at sites in this country/region.

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| | Exclusion criteria<br>Prospective study participants who meet ANY of the following criteria will not be eligible for enrollment into this study.<br>1. Receipt of treatment before the first dose of study drug (Cycle 1 Day 1) within an interval shorter than the following, as applicable:<br>• One chemotherapy or biological (e.g., antibody) cycle interval<br>• Five half-lives of any small-molecule investigational or licensed medicinal product<br>• 2 weeks, for any investigational medicinal product with an unknown half-life<br>• 4 weeks of curative radiotherapy<br>• 7 days of palliative radiotherapy<br>• 28 days of radiotherapy<br>2. Major surgery or locoregional therapy within 4 weeks of the first dose of derazantinib<br>3. Previous treatment with any FGFR inhibitor (e.g., Balversa® [erdafitinib], Pemazyre® [pemigatinib], infigratinib, rogaratinib, futibatinib, lenvatinib, ponatinib, dovitinib, nintedanib, AZD4547, LY2784455)<br>4. Unable or unwilling to swallow the complete daily dose of derazantinib capsules<br>5. Clinically unstable central nervous system (CNS) metastases (to be eligible, patients must have stable disease ≥ 3 months, confirmed by magnetic resonance imaging (MRI) or computed tomography (CT) scan, and/or have CNS metastases well controlled by low-dose steroids, anti-epileptics, or other symptom-relieving medications)<br>6. Current evidence of clinically-significant corneal or retinal disorder likely to increase the risk of eye toxicity, including but not limited to bullous/band keratopathy, keratoconjunctivitis (unless keratoconjunctivitis sicca), corneal abrasion, inflammation/ulceration, confirmed by ophthalmologic examination<br>7. Concurrent uncontrolled or active hepatobiliary disorders, untreated or ongoing complications after laparoscopic procedures or stent placement, including but not limited to active cholangitis, biloma or abscess (to be eligible, the patients have to be treated and disorders/complications should be resolved within 2 weeks prior to the first dose of derazantinib) |

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| | 8. History of significant cardiac disorders:<br>• Myocardial infarction (MI) or congestive heart failure defined as Class II to IV per the New York Heart Association (NYHA) classification within 6 months of the first dose of derazantinib (MI that occurred > 6 months prior to the first dose of derazantinib are permitted)<br>• QTcF > 450 msec for men and QTcF > 460 msec for women<br>9. Serum electrolyte abnormalities defined as follows:<br>• Hyperphosphatemia: serum phosphate > institutional upper limit of normal (ULN)<br>• Hyperkalemia: serum potassium > institutional ULN<br>• Hypokalemia: serum potassium < institutional lower limit of normal (LLN)<br>• Hypercalcemia: corrected serum calcium > 3.1 mmol/L (> 12.5 mg/dL)<br>• Hypocalcemia: corrected serum calcium < 1.75 mmol/L (< 7.0 mg/dL)<br>• Hypomagnesemia: < 0.4 mmol/L (< 0.9 mg/dL)<br>10. Significant gastrointestinal disorder(s) that could, in the opinion of the Investigator, interfere with the absorption, metabolism, or excretion of derazantinib (e.g., Crohn's disease, ulcerative colitis, extensive gastric resection)<br>11. History of additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, and *in situ* cervical cancer.<br>12. Concurrent uncontrolled illness not related to cancer, including but not limited to:<br>• Psychiatric illness/substance abuse/social situation that would limit compliance with study requirements<br>• Known uncontrolled human immunodeficiency virus (HIV) infection<br>• Severe bacterial, fungal, viral, and/or parasitic infections under treatment with therapeutic oral or intravenous (IV) medication at the time of first dose of study drug administration |

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| | 13. Blood or albumin transfusion within 5 days of the blood draw being used to confirm eligibility<br>14. Pregnant or breast feeding<br>15. Known hypersensitivity to derazantinib, or to any of the study drug excipients (starch, lactose, crospovidone, magnesium stearate). |
| **Test product, dose, mode of administration:** | Derazantinib will be supplied as 100 mg capsules.<br>A dose of 300 mg QD (three capsules of 100 mg each) of derazantinib will be administered by mouth 1 hour before, or 2 hours after, a meal. |
| **Duration of treatment:** | It is expected that most patients will receive between one and eight months of treatment with derazantinib capsules.<br>Patients will receive treatment with derazantinib capsules until death, radiographic disease progression, unacceptable toxicity, or until another of the specified criteria is met for stopping therapy. Radiographic progressive disease must be confirmed by central radiology review prior to treatment discontinuation if progression is seen on the first or second on-treatment scan.<br>In Substudy 1, if the locally-documented *FGFR2* fusion positive status was tested and not confirmed by FISH by the central laboratory designated by the Sponsor after the commencement of study treatment, these patients will be assessed on a case-by-case basis (see Section 5.7.1).<br>For patients who demonstrate continued benefit from receiving derazantinib at the time of study closure, the Sponsor aims to provide continued individual patient access to derazantinib, e.g., under a rollover study protocol, or in the context of compassionate use / named-patient access where applicable. |
| **Pharmacokinetic and pharmacodynamic variables:** | Blood samples for PD assessments of tumor markers (CA19.9, CA125, CEA), biomarkers (FGF19, FGF21, FGF23) and ctDNA will be collected and evaluated in batches either during, or at the end of, the study (see Section 6.7).<br>Blood samples for PD assessments will be collected only from patients enrolled after completion of the interim analysis, and subject to the granting of appropriate regulatory and IRB/IEC approval. These blood samples will be collected on Day 1 of Cycle 1, every 8 weeks (two cycles) for the first six cycles, once every 12 weeks (three cycles) thereafter, and at the End of Treatment visit. |

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| | Archival tumor tissue samples will be obtained for all patients to enable additional molecular analyses with regard to the identified GAs and markers predictive of response at the laboratories selected by the Sponsor (see Section 6.8).<br><br>Blood samples for sparse PK sampling will be collected on Day 1 and Day 15 of Cycle 1, and Day 1 of Cycles 2, 3 and 4, to determine the PopPK parameters of derazantinib. Exploratory assessments of metabolites of derazantinib may also be investigated from the PK plasma samples (see Section 6.6).<br><br>A subset of up to 20 patients (PK subgroup) will be asked to participate in rich PK blood sampling and PK urine sampling to assess the renal excretion of derazantinib (and its metabolites) (see Section 6.6). Patients will be asked for a additional consent to participate in the blood/urinary PK assessments.<br><br>Exploratory assessments of derazantinib (and possibly metabolites) will be investigated from the PK urine samples. |
| **Statistical methods:** | **Substudy 1**<br>To prove the drug effect over placebo in ORR in this single-arm pivotal study, the hypothesis is specified as:<br><br>H0: ORR = 0.10 and Ha: ORR=0.23.<br><br>The hypothesis test will be performed at a one-sided 2.5% significance level. A 10% response rate is chosen for the null hypothesis, which is much higher than the observed ORR of 7~8% in larger historical studies and publications (Lamarca 2014). The 23% response rate for the alternative hypothesis is estimated.<br><br>Approximately 100 patients will be enrolled for this two-stage group sequential study with futility stopping. An interim analysis for futility will be done when 40 patients who satisfied modified intent-to-treat (mITT) criteria had at least one post-baseline tumor evaluation. The study will be terminated for futility if four or fewer responses are observed among 40 evaluable patients.*<br><br>If 5 or more objective responses are observed and confirmed based on central radiology review prior to enrollment of 40 evaluable patients, the interim analysis may be performed based on fewer than 40 patients. |

* The interim analysis was conducted on 8 January 2019; futility was rejected (informative p-value 0.0275).

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| | If the treatment is ineffective, i.e., ORR=0.1, the probability of futility stopping is 63%. If the true response rate ORR=0.23, the probability of futility stopping is only 3%. The design will provide approximately 90% power to reject the null hypothesis at one-sided significance level 0.025 or equivalently to have the lower bound of confidence interval of ORR $\geq$ 10%.<br><br>All patients who receive at least one dose of derazantinib capsules will be considered evaluable for safety analyses.<br><br>**Substudy 2**<br><br>A Simon's two-stage design will be used in Substudy 2. The null hypothesis ($H_0$) that the true 3-month rate of progression-free survival (PFS3) is $p_0 \leq 0.45$ will be tested against a one-sided alternative. In the first stage, 15 mITT-evaluable patients will be accrued. If there are 7 or fewer patients with PFS 3 in these 15 patients, then Substudy 2 will be stopped. Otherwise, 28 additional mITT-evaluable patients will be accrued for a total of 43. $H_0$ will be rejected if a PFS 3 is observed in 25 or more of these 43 patients. The type I error rate is 0.0481, and power is approximately 0.8 when the true PFS3 rate for derazantinib is $p_1 = 0.65$.<br><br>All patients who receive at least one dose of derazantinib capsules will be considered evaluable for safety analyses. |
| **Data Monitoring Committee:** | The Data Monitoring Committee (DMC) will be established to ensure the safety of study patients and the validity of study results. The DMC composition and operation will be described in the DMC Charter. The DMC may recommend study termination or continuation based on periodic review of safety and/or efficacy data in this study. |

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| AE | Adverse event |
| AIC | Akaike information criterion |
| AKT | v-Akt murine thymoma viral oncogene homolog |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| ANC | Absolute neutrophil count |
| ARID1A | AT-rich interactive domain-containing protein 1A |
| ASCO | American Society of Clinical Oncology |
| AST | Aspartate aminotransferase |
| ATP | Adenosine triphosphate |
| AUC | Area under the curve |
| BAP1 | BRCA1-Associated Protein 1 |
| BIC | Bayesian information criterion |
| BRAF | v-raf murine sarcoma viral oncogene homolog |
| BUN | Blood urea nitrogen |
| CBC | Complete blood count |
| CCA | Cholangiocarcinoma |
| CDISC | Clinical Data Interchange Standards Consortium |
| CEA | Carcinoembryonic antigen |
| CFR | Code of Federal Regulations |
| cHCC-CCA | Combined hepatocellular-cholangiocarcinoma |
| CI | Confidence interval |
| CLIA | Clinical Laboratory Improvement Amendments |
| $C_{max}$ | Maximum observed plasma concentration |
| CNS | Central nervous system |
| CR | Complete response |
| CT | Computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| ctDNA | Cell-free circulating tumor deoxyribonucleic acid |
| DLT | Dose limiting toxicity |
| DMC | Data Monitoring Committee |
| DNA | Deoxyribonucleic acid |
| DoR | Duration of response |
| $EC_{50}$ | Half maximal effective concentration |
| eCCA | Extrahepatic cholangiocarcinoma |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |

| | |
|---|---|
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| EGFR | Epidermal growth factor receptor |
| ELISA | Enzyme-linked immunosorbent assay |
| EORTC | European Organization for Research and Treatment of Cancer |
| ERK | Extracellular signal-regulated kinase |
| ESA | Erythropoietin Stimulating Agents |
| FDA | Food and Drug Administration |
| FFPE | Formalin-fixed paraffin-embedded |
| FGFR | Fibroblast growth factor receptor |
| FISH | Fluorescence *in situ* hybridization |
| GA | Genetic aberration |
| GCP | Good Clinical Practice |
| G-SET | Global- Self Evaluated Transition |
| G-CSF | Granulocyte colony stimulating factors |
| GGT | Gamma-glutamyl transferase |
| $GI_{50}$ | Concentration for 50% of maximal inhibition of cell proliferation |
| GLP | Good Laboratory Practice |
| $H_0$ | Null hypothesis |
| Ha | Alternative hypothesis |
| HEK | Human embryonic kidney |
| hERG | Human ether-a-go-go-related gene |
| Hgb | Hemoglobin |
| HIPAA | Health Information Portability and Accountability Act |
| HIV | Human immunodeficiency virus |
| HRQOL | Health-related quality of life |
| HTI | Health Transition Index |
| $IC_{50}$ | Inhibitor concentrations required for 50% inhibition |
| iCCA | Intrahepatic cholangiocarcinoma |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation |
| IDH | Isocitrate dehydrogenase |
| IEC | Independent ethics committee |
| IHC | Immunohistochemistry |
| INR | International normalized ratio |

| | |
|---|---|
| IRB | Institutional review board |
| IRT | Interactive Response Technology |
| IV | Intravenous |
| IVDD | In Vitro Diagnostics Directive |
| $K_i$ | Inhibitory constant |
| KM | Kaplan-Meier |
| KRAS | Kirsten rat sarcoma viral oncogene homolog |
| LDH | Lactate dehydrogenase |
| LFT | Liver function tests |
| LLN | Lower limit of normal |
| MAPK | Mitogen-activated protein kinases |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MEK | Tyrosine/threonine kinase |
| MI | Myocardial infarction |
| mITT | Modified intent-to-treat |
| MRI | Magnetic resonance imaging |
| MTD | Maximum tolerated dose |
| NA | Not applicable |
| NCI | National Cancer Institute |
| NE | Not evaluated |
| NGS | Next-Generation Sequencing |
| nM | Nanomolar |
| NOAEL | No-observed-adverse-effect level |
| NSTD | Non-severely toxic dose |
| NYHA | New York Heart Association |
| ORR | Objective response rate |
| OS | Overall survival |
| pCCA | Perihilar cholangiocarcinoma |
| PD | Progressive disease |
| PD | Pharmacodynamic(s) |
| PFS | Progression-free survival |
| PFS 3 | Progression-free survival at 3 months |
| P-gp | P-glycoprotein |
| PI3K | Phosphatidylinositol 3-kinase |
| PK | Pharmacokinetic(s) |
| PKC | Protein kinase C |
| PLCγ | Phospholipase Cγ |
| PopPK | Population pharmacokinetics |
| PR | Partial response |

| | |
|---|---|
| PT | Preferred term |
| PT | Prothrombin time |
| PTT | Partial prothrombin time |
| QD | Once daily |
| QOD | Once every other day |
| QOL | Quality of life |
| RBC | Red blood cell |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RNA | Ribonucleic acid |
| ROS1 | ROS proto-oncogene 1 |
| RP2D | Recommended Phase 2 dose |
| RTK | Receptor tyrosine kinase |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SD | stable disease |
| SEER | Surveillance, Epidemiology, and End Results |
| SOC | Standard of care |
| SOP | Standard Operating Procedure |
| SPF | Sun Protection Factor |
| STAT | Signal transducers and activator of transcription |
| STD | Severely toxic dose |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TACE | Transarterial chemoembolization |
| TEAE | Treatment-emergent adverse event |
| TGI | Tumor growth inhibition |
| $T_{max}$ | Time to maximum observed concentration |
| TP53 | Tumor protein p53 |
| TTP | Time to progression |
| ULN | Upper limit of normal |
| US | United States |
| VAS | Visual analog scale |
| VEGFR | Vascular endothelial growth factor receptor |
| WBC | White blood cell |
| WBMRI | Whole-body magnetic resonance imaging |

# 1 INTRODUCTION

Cholangiocarcinoma (CCA) is the most common malignant tumor of the biliary tract, affecting approximately 2,500 patients annually in the United States (US), with an average incidence of 1.67 patients per 100,000 people per year (NORD 2015). Emerging at any portion of the biliary tree, it includes tumor subtypes that differ in etiology, pathophysiology, clinical presentation, and management. Depending on the anatomic location, CCA is classified as intrahepatic (iCCA) and extrahepatic (eCCA), which are further classified into perihilar (pCCA) or distal tumors. iCCA originates from the intrahepatic biliary ductal system and accounts for 10-20% of primary hepatic malignancies (Blechacz 2008, NCCN 2016).

There are a number of known potential risk factors for iCCA, including primary sclerosing cholangitis, hepatolithiasis, and liver fluke. However, these factors are not universally identified in most patients diagnosed with iCCA. Due to anatomic location, iCCA is usually diagnosed at a later stage than eCCA and has very limited treatment options. The iCCA tumor biology is not well-understood; however, genomic profiling with whole-exome and Next-Generation Sequencing (NGS) or fluorescence *in situ* hybridization (FISH) has identified multiple molecular aberrations that may contribute to its carcinogenesis (Chong 2016, Sia 2015, Graham 2014, Borad 2014). Recent whole genome sequencing efforts have identified known mutations in genes such as epidermal growth factor receptor (*EGFR*), kirsten rat sarcoma viral oncogene homolog (KRAS), v-raf murine sarcoma viral oncogene homolog (*BRAF*) and tumor protein p53 (*TP53*), novel mutations in isocitrate dehydrogenase (*IDH*), BRCA1-Associated Protein 1 (*BAP1*) and AT-rich interactive domain-containing protein 1A (*ARID1A*), and novel fusions such as fibroblast growth factor receptor 2 (*FGFR2*) and ROS proto-oncogene 1 (*ROS1*). Inhibitors of these pathways are currently in clinical development (Chong 2016).

Patients diagnosed at an early stage of iCCA are candidates for curative resection or liver transplantation. Liver transplantation remains the treatment of choice with the best outcome as it intends to cure the disease, but due to the scarcity of organs it is restricted to very few patients (ACS 2012). Unfortunately, as mentioned above, iCCA is asymptomatic in the early stages and by the time it is diagnosed, most patients present with an advanced stage of the disease. Advanced disease means most patients (approximately 90%) are not eligible for curative surgery, leading to an overall survival of approximately 6 months.

Non-surgical treatment options for advanced iCCA include locoregional therapy such as transarterial chemoembolization (TACE) and chemotherapy with or without radiation therapy. The current non-surgical standard of care for unresectable iCCA is combination chemotherapy with gemcitabine plus cisplatin (Okusaka 2010, Khan 2012). Other systemic chemotherapy options include capecitabine, oxaliplatin, fluoropyrimidines, or a combination of these agents. It should be noted that none of these drugs have been approved for the treatment of iCCA (ACS 2012, Eckel 2011, Kondo 2008, NCCN 2016). Disappointingly, even combined multi-agent chemotherapy does not offer a durable response in patients with advanced iCCA, and only 5–10% of patients survive 5 years after diagnosis (Anderson 2004).

Intrahepatic CCA is a rare malignancy that continues to present challenges in diagnosis and treatment, is associated with a poor prognosis, and is often compounded by background biliary tract and/or liver disease. In the US, the incidence and mortality of iCCA have increased over the last 30 years without clear underlying etiological reasons. While improvements in diagnostic modalities and chemotherapy have allowed for detection at earlier stages and greater survival rates, the prognosis is still unfavorable (Blechacz 2008).

## 1.1 Therapeutic rationale

*FGFR*s, like other receptor tyrosine kinases, are activated by tyrosine phosphorylation and signal through multiple signal transduction pathways, including mitogen-activated protein kinases (*MAPK*), phosphatidylinositol 3-kinase (*PI3K*), phospholipase Cγ (*PLCγ*), protein kinase C (*PKC*), and signal transducers and activator of transcription (*STAT*). Activation leads to a series of cellular signaling events including increased cellular proliferation, differentiation and migration (Turner 2010, Kelleher 2013). The *FGFR* pathway has also been implicated in normal physiological processes such as mesodermal patterning of the embryo, wound healing, and angiogenesis (Turner 2010).

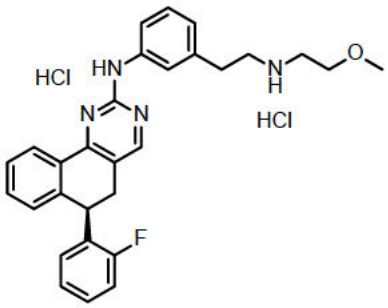
*FGFR* dysregulations such as fusions, amplification, and mutations are frequently observed in human cancers, including iCCA. Gene fusions of *FGFR2* with multiple partners have been discovered in several recent studies of patients with iCCA and other cancers. *FGFR2* fusions have been identified as a novel oncogenic, druggable target in up to 45% of iCCA samples; this suggests that oncogenic activation of *FGFR2* may represent a potential target for tyrosine kinase inhibitor therapies (Arai 2014, Borad 2014, Borad 2015, Graham 2014, Ross 2014, Sia 2015, Wu 2013).

## 1.2 Investigational product description

Chemical name: (R)-6-(2-fluorophenyl)-N-(3-(2-((2-methoxyethyl)amino)ethyl)phenyl)-5,6-dihydrobenzo[h]quinazolin-2-amine dihydrochloride

Appearance: Derazantinib•2 HCl is a yellow powder

Structural formula:




Molecular Formula $C_{29}H_{31}Cl_2FN_4O$

Molecular weight: 541.49 g/mol

## 1.3 Proposed indication and dosage

Derazantinib is indicated for the treatment of patients with *FGFR2* fusion positive inoperable or advanced iCCA. A Phase 1/2 study (ARQ 087-101) in solid tumors with *FGFR* genetic aberrations (GAs), including iCCA with *FGFR2* fusion has completed enrollment, with a total of 119 patients. Derazantinib capsules will be administered by mouth 1 hour before, or 2 hours after, a meal at a dose level of 300 mg once daily (QD).

## 1.4 Nonclinical data

Derazantinib is a multi-kinase inhibitor with potent *FGFR*1, 2, and 3 activity. Supporting *in vitro* and *in vivo* studies are summarized below.

### 1.4.1 Nonclinical pharmacology overview

#### *1.4.1.1 In vitro studies*

*1.4.1.1.1 Biochemistry: Inhibition of FGFR kinase activity of derazantinib*

FGFR kinase biochemical assays were performed. Derazantinib selectivity against all four FGFR isoforms was assayed. Derazantinib inhibited wild-type FGFR1, FGFR2, and FGFR3 with biochemical inhibitor concentration required for 50% inhibition ($IC_{50}$) values in the 1.8 to 4.5 nM range and FGFR4 with somewhat lower potency ($IC_{50}$ value of 34.3 nM) (TR-087-048). Enzymatic kinetic experiments for derazantinib with both FGFR1 and FGFR2 were performed. The inhibition constant ($K_i$) values were determined to be 2.7 ± 0.2 nM and 0.68 ± 0.07 nM, respectively, demonstrating strong affinity of derazantinib for FGFR1 and FGFR2. Michaelis-Menten graphs were generated and four inhibition modes (competitive, uncompetitive, noncompetitive, and mixed) were evaluated in both Akaike information criterion (AIC) and Bayesian information criterion (BIC) to determine the best fitting model. After the analyses, the competitive model received the lowest AIC and BIC and the heaviest weight of AIC and BIC which indicates that derazantinib profiled as a competitive inhibitor for both FGFR1 and FGFR2 (data on file). The data which indicate that derazantinib is a competitive inhibitor for both FGFR1 and FGFR2 are further strengthened by the fact that the values for the α-factor approached infinity in both cases (data on file). It was therefore concluded that derazantinib is an adenosine-triphosphate-(ATP)-competitive inhibitor for both FGFR1 and FGFR2.

Activation of FGFR kinases requires autophosphorylation on multiple tyrosine residues (Lew 2009, Furdui 2006). Inhibition of this autoactivation reaction by derazantinib was evaluated by titrating increasing concentrations of the inhibitor with unphosphorylated FGFR1 and FGFR*2* kinases in an autophosphorylation assay. Derazantinib inhibited the autophosphorylation of FGFR1 and FGFR2 in a dose-dependent manner. This observation suggests that, in addition to inhibiting the active form of the kinase, derazantinib binds to its unphosphorylated or inactive form, thus delaying its activation.

To understand the selectivity of derazantinib across the kinome, the compound was tested against a panel of 298 kinases at a concentration of 0.1 µM. Among the 298 kinases assayed, approximately 50 (including FGFR1, FGFR2, FGFR3, and FGFR4) were inhibited by greater than 50% by derazantinib (TR-087-049). In this subset of kinases, examination of $IC_{50}$ values revealed that 19 kinases (excluding FGFRs) exhibited sensitivities to derazantinib within a 3- to 10-fold range of the $IC_{50}$ value for FGFR2.

*1.4.1.1.2 Anti-proliferative effect and FGFR pathway inhibition by derazantinib in human cancer cell lines*

To determine whether derazantinib inhibits the phosphorylation of FGFR1, FGFR2, FGFR3, and FGFR4 in cells, full-length FGFR1, FGFR2, FGFR3, and FGFR4 was ectopically expressed in COS-1 cells and the effect of derazantinib on phosphorylation of FGFRs was examined. It was found that derazantinib inhibited the phosphorylation of FGFR1, FGFR2, and FGFR3 with half maximal effective concentration ($EC_{50}$) values of < 0.123 µM, 0.185 µM, and 0.463 µM, respectively. Derazantinib did not inhibit the phosphorylation of FGFR4 in this overexpression system ($EC_{50}$ > 10 µM). The anti-proliferative effect of derazantinib was also examined in a panel of Ba/F3 cell lines that had been engineered to be dependent on individually overexpressed tyrosine protein kinases for survival, including cell lines dependent on individual FGFR isoforms and *FGFR* fusions. The concentration for 50% of maximal inhibition of cell proliferation ($GI_{50}$) values for Ba/F3-FGFR1, Ba/F3-FGFR2, Ba/F3-FGFR3, and Ba/F3-FGFR4 ranged between 232 nM and 1346 nM, with Ba/F3-FGFR2 the most sensitive cell line to derazantinib followed by Ba/F3-FGFR1 and Ba/F3-FGFR3. FGFR fusions were also examined in the Ba/F3 system, including TEL-FGFR2, FGFR2-AAF3, FGFR2-BICC1, FGFR2-CASP7, FGFR2-CCDC6, FGFR2-CCDC6, and FGFR3-BAIAP-2L1. The $GI_{50}$ values were between 39.9 nM and 1121 nM, with FGFR3-BAIAP2L1 being the most sensitive cell line.

Anti-proliferative activity of derazantinib was evaluated on five cholangiocarcinoma (CCA) cell lines (OZ, NOZ, HuCCT1, HCCC9810, and HuH28) and two adrenocortical cell lines (NCI-H295R and SW 13). The results showed that in all cell lines cell growth was potently inhibited by derazantinib with $IC_{50}$ values ranging from 1.4 to 3.9 µM. These results suggest that CCA and adrenocortical carcinoma could be therapeutic indications for derazantinib (TR-087-107).

### *1.4.1.2 In vivo studies*

*1.4.1.2.1 Evaluation of derazantinib in human and murine xenografts of various histological types in athymic mice*

The *in vivo* anti-tumor effect of derazantinib was assessed in athymic mice bearing Ba/F3-FGFR2, Ba/F3-INSR, SNU-16, and NCI-H716 cell line-derived tumors. The Ba/F3-FGFR2 and Ba/F3-INSR are transfected models. The SNU-16 cell line harbors amplified *FGFR2* and contains a *PDHX-FGFR2* fusion, while the NCI-H716, also amplified for *FGFR2*, contains an *FGFR2-COL14A1* fusion. Derazantinib demonstrated potent tumor growth inhibition (TGI) in the Ba/F3-FGFR2 model, while failing to inhibit the growth of the Ba/F3-INSR model. Meaningful (> 50 TGI vs. control) tumor inhibition was observed in both cancer cell line derived xenograft models. In the SNU-16 xenograft study, treatment with 75 mg/kg and 50 mg/kg achieved 83% (p=0.002) and 69% (p=0.013) TGI, respectively. Partial and complete regressions were also observed in both dose groups. In the NCI-H716 human cecum model, 50 mg/kg and 75 mg/kg on a Q1Dx14 schedule demonstrated significant TGI of 68% (p = 0.0001) and 96% (p = 0.0001), respectively. Doses of 150 mg/kg of derazantinib were not well tolerated, resulting in unacceptable weight loss and general lethargy.

#### *1.4.1.3 In vivo pharmacodynamics*

The *in vivo* pharmacodynamic effect of derazantinib was examined in NCI-H716, SNU-16, and MFM-223 tumor-bearing animals. A single dose of derazantinib led to a reduction in phospho-FGFR, phospho-FRS2α, phospho-ERK (extracellular signal-regulated kinase), phospho-AKT (v-Akt murine thymoma viral oncogene homolog), and phospho-S6 in all three models tested, while the total FGFR2 protein was unaffected by derazantinib treatment. These results indicate that a single dose of derazantinib was sufficient to attenuate FGFR signaling in NCI-H716, SNU-16, and MFM-223 xenograft tumors (TR-087-040, TR-087-079, TR-087-080).

Evidence of derazantinib target engagement can be detected by measuring the inhibition of phosphorylation of derazantinib target receptor tyrosine kinase (RTK) as well as key downstream signaling proteins. In nonclinical xenograft tumor models, inhibition of the phosphorylation of FGFR, FRS2α, and ERK was observed using immunohistochemistry (IHC) staining on SNU-16 tumors at the repeated, efficacious dose of 75 mg/kg (TR-087-047). By Western blotting analysis, tyrosine/threonine kinase (MEK) and ERK phosphorylation levels were reduced by 68% and 82%, respectively. This dose resulted in plasma levels of derazantinib of 4.9 ± 2.3 μM.

#### *1.4.1.4 Nonclinical pharmacokinetic studies*

The pharmacokinetics and toxicokinetics of derazantinib were characterized in rats and dogs. The oral bioavailability of derazantinib in rats was 37%, and in dogs ranged from 38 to 46% (solution or powder filled capsule), respectively. Overall, in 28-day repeat dose studies (in both species), derazantinib had a half-life in plasma which ranged from 4 to 10 hours and time to maximum observed concentration ($T_{max}$) which ranged from 5 to 16 hours. Derazantinib was not consistently dose proportional and was found to accumulate after repeat dosing in these species.

### 1.4.2 Nonclinical toxicology studies

Derazantinib was well tolerated over the course of the 13 weeks in Good Laboratory Practice (GLP) toxicity studies, with no-observed-adverse-effect levels (NOAELs) of 10 mg/kg/day for rats and dogs being determined. In the 28-day GLP toxicity studies, a NOAEL dose of 20 mg/kg/day (18 days) was determined in dogs, and a non-severely toxic dose (NSTD) of 15 mg/kg/day was determined in rats. A severely toxic dose (STD) in rats was determined to be 50 mg/kg/day.

The toxicity profile of orally administered derazantinib in rats and dogs was characterized principally by decreases in body weight and/or body weight gain, an effect generally correlated to a decrease in food consumption. Trends in reversibility during the recovery phase were observed for decreases in body weight and/or body weight gain and decreased food consumption in dogs but not in rats. Target organ toxicities based on the results of the 28-day rat and dog studies were associated with those involving gastrointestinal (rat, dog), hematological (rat, dog), liver (rat, dog), bone (rat) and lung (rat) function.

In the 28-day rat study, all control, low, and mid dose (0, 5, and 15 mg/kg) animals survived to the scheduled terminal necropsy. All high dose (50 mg/kg) animals, excluding those designated for recovery, were sacrificed and/or necropsied between Days 12 and 14 of the dosing phase. Derazantinib-related clinical observations were limited to animals given

50 mg/kg/day, which made necessary the suspension of further dosing and unscheduled terminal necropsy. These clinical observations, along with decreases in body weight/body weight gain and food consumption, included hunched appearance and swelling of the abdomen (noted in one female), thinness, nasal and oral discharge, fecal abnormalities (few and non-formed), squinting of the eyes, and pelage/skin abnormalities. Clinical observations associated with thinness, decreases in body weight/body weight gain did not resolve following the 2-week recovery phase for animals given 50 mg/kg/day.

Additionally, in the 28-day rat study, derazantinib administration was associated with several effects on clinical pathology test results. The most toxicologically important effects included reduced erythropoiesis at >15 mg/kg/day, suspected lymphoid tissue injury at 50 mg/kg/day (females), and liver injury at >15 mg/kg/day. Specifically, reduced erythropoiesis was associated with decreased red cell mass and absolute reticulocyte counts as well as changes in erythrocytic indices. Decreased lymphocyte counts were observed in females given 50 mg/kg/day. Increased alanine aminotransferase (ALT) activity was first observed in males given 5 mg/kg/day, followed by increased ALT and alkaline phosphatase (ALP) activity in animals given 15 mg/kg/day. At dose levels of 50 mg/kg/day, increased ALT, aspartate aminotransferase (AST), ALP, and gamma-glutamyl transferase (GGT) activities were observed. A few less specific derazantinib-related effects, especially changes in electrolyte values, were observed during the recovery phase in animals given 50 mg/kg/day. These changes may have been associated with mild dehydration. No macroscopic findings were attributed to derazantinib at the terminal or recovery necropsy.

In animals sacrificed in moribund condition or at the terminal sacrifice, derazantinib-related microscopic findings were observed in the femur and sternum bone marrow, alimentary canal (tongue, esophagus, nonglandular stomach, duodenum, ileum, and jejunum), spleen, and lung. Most findings were limited to the 50 mg/kg/day dose level. Exceptions were the lung and spleen, where findings were also observed at 15 mg/kg/day. All derazantinib related microscopic findings observed at the terminal necropsy and in animals sacrificed at an unscheduled interval were reversed at the recovery necropsy, excluding femur and sternum physeal hypertrophy, increased splenic extramedullary hematopoiesis, and lung vacuolated macrophage infiltrates. Tongue and esophageal ulcers observed at 50 mg/kg/day were considered severely toxic.

In the 28-day dog study, administration of derazantinib was tolerated as an oral capsule administration in dogs at 3 and 10 mg/kg/day for 29 days and at 20 mg/kg/day for 18 days; however, it was not tolerated at 30 mg/kg/day for 7 days. Animals given 30 mg/kg/day had vomitus, abnormal feces, body weight loss, and/or markedly reduced food consumption during the first week of dosing. One male given 30 mg/kg/day was sacrificed on Day 6 of the dosing phase in moribund condition that included clinical observations of vomitus, limited use of the hind quarters, ataxia, rigid stance, hypoactivity, dilated and minimally responsive pupils, excessive salivation, occasional tonic front limbs, and postictal and close to seizure threshold. The male had clinical pathology findings consistent with inflammation/stress, dehydration, and lower serum potassium and chloride that likely resulted from vomiting. Potentially adverse, derazantinib-related microscopic findings of acute inflammation and ulceration of the esophagus were also noted, and the moribund condition of the male is partially attributed to these microscopic findings.

All other animals survived to their scheduled sacrifices. Due to adverse findings observed at 30 mg/kg/day, dosing was suspended on Day 8 and resumed on Day 12 of the dosing phase at 20 mg/kg/day. Abnormal feces observed for most animals given 20 mg/kg/day was not considered to be an adverse reaction because it did not impact the health of the animals. Animals given 30/20 mg/kg/day had white discolored haircoat of the entire head during the dosing and recovery phases; however, this observation was not adverse, and no corresponding microscopic finding was present. No derazantinib-related changes in electrocardiogram (ECG) parameters or ophthalmic examinations were observed. No derazantinib-related clinical pathology effects were observed at 3 or 10 mg/kg/day. A few potentially derazantinib-related findings in animals given 30/20 mg/kg/day were minor and not considered adverse or toxicologically important. Potentially adverse, derazantinib-related microscopic findings of acute inflammation and ulceration of the esophagus occurred in one male given 30/20 mg/kg/day. Derazantinib related microscopic findings noted during the dosing phase were not present in recovery animals.

In rats and dogs in 28-day/4-week studies, no apparent derazantinib-related effect was noted following the dosing phase examination. However, of note, two male rats (Animal Nos. B84426 and B84424) given 5 mg/kg/day, one male given 15 mg/kg/day (Animal No. B84442), and a female (Animal No. B84516) given 15 mg/kg/day, were seen to have corneal dystrophy on Day 26 of the dosing phase. This finding is not considered derazantinib-related due to its low incidence and lack of microscopic correlation.

In 28-day rat studies, minimal to slight physeal hypertrophy was an increase in the thickness of the physis mostly due to enlargement and mild disorganization of the zone of hypertrophy. Minimal physis hypertrophy persisted in the femur of two recovery males and one female given 50 mg/kg/day and in the sternum of one recovery female given 50 mg/kg/day.

Transient effects on clinical chemistry such as increased glucose levels and phosphorous levels were observed in rats and/or dogs in shorter duration 7-day repeat dose toxicity studies and may be characteristic of *FGFR* kinase inhibitors (Cuevas-Ramos 2009, Kharitonenkov 2011, Brown 2005).

In 13-week toxicity studies, 1, 3, or 10 mg/kg/day doses of derazantinib were well tolerated when administered daily via oral gavage to Sprague Dawley rats for 13 weeks. Derazantinib-related findings included minimal differences in red blood cell indices; minimally lower total white blood cell count, due to lower absolute lymphocyte and monocyte counts (females); and minimally lower albumin concentration in animals administered 10 mg/kg/day. Findings for animals administered ≥ 3 mg/kg/day included minimally higher cholesterol concentration (female) and vacuolated macrophage infiltrates in the alveoli of the lung; at the recovery sacrifice, these persisted in the lung of males administered 10 mg/kg/day and were partially reversed in females administered 10 mg/kg/day. As none of these observations were considered adverse, the NOAEL is 10 mg/kg/day via oral gavage. At the end of the dosing phase, the NOAEL of 10 mg/kg/day corresponded to combined male and female average peak concentration ($C_{max}$) and area under the concentration-time curve from 0 to 24 hours post dose ($AUC_{0-24}$) values of 293 ng/mL and 5660 ng·hr/mL, respectively.

In 13-week toxicity studies, 1, 3, or 10 mg/kg/day doses of derazantinib were well tolerated when administered daily via capsule to beagle dogs for 13 weeks. Derazantinib-related findings included increased lymphocytes in the left and/or right nictitating membranes of animals administered ≥ 3 mg/kg/day, which were mostly reversed by the end of the recovery phase, and minimally decreased red cell mass (males and females), absolute reticulocyte count (females), and minimally increased AST and ALT activities (females), without histological correlates, in animals administered 10 mg/kg/day. The NOAEL is 10 mg/kg/day via capsule. At the end of the dosing phase, the NOAEL of 10 mg/kg/day corresponded to combined male and female $C_{max}$ and $AUC_{0-24}$ values of 444 ng/mL and 6680 ng·hr/mL, respectively, for males and females combined.

Derazantinib was evaluated for effects on the human ether-a-go-go-related gene (hERG) potassium channel using human embryonic kidney (HEK)293 cells transfected with hERG. Conflicting *in vitro* hERG results were obtained between two laboratories. In one study, the hERG $IC_{50}$ for derazantinib was greater than 3 µM, whereas in the second study it was 0.06 µM. Consequently, a dog telemetry study was conducted to further examine any cardio effects of derazantinib. There were no notable effects of derazantinib on pulse pressure, PR interval, QRS duration, QTcVDW interval, or arrhythmogenesis. No effect on QT was observed in dogs in the cardiovascular study (60 mg/kg) or in the ECG in the 28-day and 13-week toxicity studies (up to 30/20 mg/kg).

Derazantinib was found to have phototoxic potential in the 3T3 Neutral Red Uptake Phototoxicity Test.

In genotoxicity assays, derazantinib was negative for mutagenicity in an AMES study, but positive via a predominantly aneugenic mode of action in an *in vitro* micronucleus assay. In a subsequent *in vivo* micronucleus assay in rats, evaluating both clastogenicity and aneugenicity, derazantinib was demonstrated to not be genotoxic.

## 1.5 Clinical experience

ARQ 087-101, entitled 'A Phase 1/2 Study of ARQ 087 in Adult Subjects with Advanced Solid Tumors with *FGFR* Genetic Alterations, Including Intrahepatic Cholangiocarcinoma with *FGFR2* Gene Fusion', was an open-label, two-part Phase 1/2, dose escalation, and signal finding study of derazantinib capsules administered to patients with advanced solid tumors. The study was designed to explore the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of derazantinib, and to define a recommended Phase 2 dose (RP2D).

Further PK analyses were performed in study DZB-CS-102, entitled 'A Phase 1, two-part, open-label, single-oral-dose study to investigate the absolute bioavailability and absorption, pharmacokinetics, distribution, metabolism, and excretion of [$^{14}$C]-derazantinib in healthy male subjects' (see Section 1.5.4).

### 1.5.1 ARQ 087-101 Part 1: Dose escalation/food-effect cohorts

Part 1 was the first-in-human part of the open-label clinical study with derazantinib capsules. Adult patients with advanced solid tumors whose cancer had progressed following standard therapy, or who had been unable to tolerate standard therapy, and/or for

whom no standard treatment was available, were enrolled. The study was conducted to evaluate the safety, tolerability, PD, and PK of derazantinib in patients with advanced solid tumors. Treatment was initiated at a dose level of 25 mg every other day (QOD) under fasted conditions (1 hour prior to, or 2 hours after, the meal).

Dose escalation was done according to the standard 3+3 dose escalation schema. The maximum tolerated dose (MTD) was defined as the dose level at which no more than one patient with a dose limiting toxicity (DLT) was observed among six patients. Assessment of tumor response was performed according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 at baseline and every two cycles (a cycle was defined as a 28-day period). Safety assessments included physical examination, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, and hematology/biochemistry. Treatment-emergent adverse events (TEAEs) were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

The study was initiated with a derazantinib dose of 25 mg QOD. Based on the drug safety profile and no significant difference in derazantinib PK exposure compared to higher dose levels (up to 425 mg QD), including the Food-effect Cohort PK data, 300 mg QD under fasted conditions (1 hour prior to, or 2 hours after, the meal) was defined as the RP2D and recommended for further evaluation in Part 2 (Expanded Cohort) of the study.

In total, 80 patients were enrolled and treated in Part 1 at four sites in the US. All patients received at least one dose of derazantinib.

### 1.5.2 Part 2: Expanded cohort/signal confirmation

Once the RP2D was determined, patients with advanced solid tumors with *FGFR* GAs, including iCCA with *FGFR2* fusions, were enrolled in Part 2. All patients in Part 2 received at least one dose of derazantinib capsules at the RP2D level of 300 mg QD (1 hour prior to or 2 hours after the meal).

As of 26 October 2018, study ARQ 087-101 had completed a total enrollment of 119 patients, none of whom were ongoing. Enrollment into the study (Part 1 and Part 2) is completed, and the clinical study report for the entire study is being prepared.

### 1.5.3 Part 1/Part 2 safety analysis

As of 26 October 2018, enrollment in study ARQ 087-101 had been completed, with a total of 119 patients enrolled and evaluated for the safety and tolerability of derazantinib. 61 patients were enrolled in Dose Escalation / Food Effect cohorts: three were dosed at 25 mg QOD, six at 25 mg QD, six at 50 mg QD, four at 100 mg QD, five at 150 mg QD, five at 200 mg QD, seven at 250 mg QD, six at 325 mg QD, seven at 425 mg QD, five at 400 mg QD, and an additional seven patients were dosed at 400 mg QD under fed conditions. The RP2D was defined as 300 mg QD.

Due to dose-dependent increases in the overall number of drug-related AEs and no significant difference in derazantinib PK exposure compared to higher dose levels (up to 425 mg QD), the dose of 300 mg QD was defined as the RP2D. There were three events of CTCAE Grade 3 AST increased that were defined to be a DLT. All these events resolved

after dose reduction (one patient) or treatment discontinuation (two patients). The first event was observed at a dose level of 250 mg QD (dose was reduced to 200 mg QD) and the two other events were observed at 425 mg QD. No DLTs were reported in the 12 patients treated at the dose level of 400 mg QD with or without food. However, there was an increase in the number of drug-related AEs at high dose levels (400–425 mg QD) compared to medium dose levels (250–325 mg QD), thus the dose of 300 mg QD was defined as RP2D. Additionally, at near steady state conditions (Day 22), derazantinib concentrations are dose proportional in the dose range of 100 to 300 mg QD dosing which supports a manageable and predictable dose reduction plan from 300 to 200 mg QD and from 200 to 100 mg QD.

A total of 58 patients were enrolled and treated at the RP2D level. The enrollment of patients with advanced solid tumors with *FGFR* GAs was completed in January 2017. All patients had discontinued treatment as of 26 October 2018. The most common reasons for discontinuing treatment were radiological disease progression (per RECIST) 69/119 (58.0%) and clinical disease progression 24/119 (20.2%).

At least one drug-related AE was reported in 102 of 119 patients (85.7%), with most being mild or moderate in severity. The five most common derazantinib-related AEs were nausea (42.9%), fatigue (41.2%), AST increased (26.1%), vomiting (21.8%), and diarrhea (21.0%). Derazantinib-related severe (≥ CTCAE grade 3) AEs were reported in 23/119 patients (19.3%).

Serious adverse events (SAEs) were reported in 34/119 (28.6%) patients. Four patients (4/119, 3.4%) experienced drug-related SAEs, including stomatitis, upper gastrointestinal hemorrhage, electrocardiogram QT prolongation, and abnormal ECG (each in one patient).

Eleven events (all assessed as unrelated) were reported with fatal outcome; in six cases, the events were reported as disease progression, two were reported as general physical health deterioration, and three events were reported as cardiomyopathy, cachexia, and pneumonia.

Overall, at 300 mg QD dose level, derazantinib demonstrated a manageable safety profile, with most derazantinib-related AEs being of CTCAE Grade 1–2, and provided adequate exposure to ensure patient response, along with predictable exposure in the event a dose reduction is necessary.

### 1.5.4 Phase 1 PK study (DZB-CS-102) in healthy subjects

Following a single oral 300 mg dose of radiolabeled [$^{14}$C]-derazantinib in the Phase 1 human absorption, distribution, metabolism, and excretion study DZB-CS-102, 76.5% of the dose was recovered in feces and 6.62% in urine, indicating that fecal excretion was the main route of elimination. As renal excretion was the minor route of elimination in healthy subjects, it is expected that renal excretion would also be the minor elimination route for subjects with renal impairment following oral dosing. The metabolite profiling in feces is ongoing.

### 1.5.5 ARQ 087-101 *FGFR2*-fusion positive iCCA patients

As of 26 October 2018, a total of 29 patients with *FGFR2*-fusion positive iCCA had been enrolled and treated with derazantinib capsules in study ARQ 087-101. *FGFR*2 GA status was based on locally performed NGS or fluorescent *in-situ* hybridization (FISH). In the

29 patients with *FGFR2*-fusion positive status, six patients had a partial response (21%), the disease control rate (partial response or stable disease as best objective response) was 83%, and the median progression-free survival was 5.7 months (Mazzaferro 2018).

### 1.5.6 ARQ 087-101 *FGFR2*-mutation/amplification positive iCCA patients

As of 26 October 2018, a total of six patients with *FGFR2*-mutation/amplification positive iCCA had been enrolled and treated with derazantinib capsules in study ARQ 087-101. *FGFR*2 GA status was based on locally performed NGS. In the six patients with *FGFR2*-mutation/amplification positive status, no patients had a partial response, four patients had some degree of tumor shrinkage per RECIST 1.1, the disease control rate (partial response or stable disease as best objective response) was 67%, and the median progression-free survival was 6.7 months (Droz dit Busset 2020).

Detailed nonclinical and clinical data can be found in the derazantinib Investigator's Brochure.

# 2 STUDY OBJECTIVES

## 2.1 Primary objective

**Substudy 1**

To evaluate the anti-cancer activity by Objective Response Rate (ORR) by central radiology review as per RECIST version 1.1 in patients with inoperable or advanced iCCA whose tumors harbor *FGFR2* fusions (by FISH performed by the central laboratory) and who received at least one prior regimen of systemic therapy.

**Substudy 2**

To evaluate the anti-tumor activity of derazantinib by progression-free survival at 3 months (PFS 3) based on survival status or central radiology review (RECIST version 1.1) in patients with inoperable or advanced iCCA whose tumors harbor *FGFR2* mutations or amplifications, and who received at least one prior regimen of systemic therapy.

## 2.2 Secondary objectives

**Substudy 1 and Substudy 2**

- To evaluate progression free survival (PFS) by central radiology review and overall survival (OS)
- To evaluate duration of response (DoR) by central radiology review
- To evaluate the safety profile (toxicities) of derazantinib in this patient population
- To evaluate changes, and assess the minimally important difference, in health-related quality-of-life (HRQOL) and symptom response from baseline using the EORTC QLQ-C30, QLQ-BIL21, Global Self Evaluated Transition (G-SET) / Health Transition Index (HTI), and the EQ-5D visual analog scale (VAS)

**Substudy 2**

- To evaluate the anti-cancer activity by ORR by central radiology review as per RECIST version 1.1 in patients with inoperable or advanced iCCA whose tumors harbor *FGFR2* mutations or amplifications, and who received at least one prior regimen of systemic therapy

## 2.3 Exploratory objectives

The exploratory objectives of this study are:

- To evaluate changes in pharmacodynamic (PD) biomarkers
- To evaluate ORR, PFS, OS, and DoR by PD biomarkers
- To evaluate the relationship between derazantinib exposure and effectiveness, toxicity and PD biomarkers
- To explore the concordance of a liquid biopsy diagnostic test compared to baseline tumor biopsy
- To evaluate population pharmacokinetics (PopPK)
- To evaluate the urinary excretion of derazantinib, and possibly its metabolites, in a subset of patients
- To compare TTP on the first and/or the last prior line of systemic therapy (reported) versus TTP on derazantinib by central radiology review (TTP will be calculated from the first date of receiving study drug or prior line of systemic therapy until radiographic disease progression)

# 3 INVESTIGATIONAL PLAN

## 3.1 Overall study design and plan

This is a multi-center, open label, single arm study evaluating derazantinib in adult patients with inoperable or advanced iCCA and *FGFR2* GAs.

- **Substudy 1** enrolls patients with *FGFR2* fusions.
- **Substudy 2** enrolls patients with *FGFR2* mutations/amplifications (see Appendix 8).
- A subset of up to 20 patients (PK/biomarker subgroups) will be asked to participate in a rich PK blood sampling and PK urine sampling to assess the renal excretion of derazantinib (see Section 6.6).

Substudy 1 is considered pivotal and will enroll approximately 100 patients to determine the ORR (see Section 10.7).

Substudy 2 will use a Simon's two-stage design, with approximately 15 mITT-evaluable patients in Stage 1, and an additional 28 mITT-evaluable patients if the study proceeds to Stage 2.

Patient eligibility may be assessed in two steps: 1) molecular pre-screening to confirm *FGFR2* GA status (see Section 5.2); clinical screening procedures to confirm study treatment eligibility (see Section 5.3).

Molecular pre-screening for *FGFR2* fusions in Substudy 1 may be based on local or central testing (see Section 6.8.1, Table 1). If pre-screening is performed based on a local test, then a central confirmation by the *FGFR2* break-apart FISH Probe Kit test is required for Substudy 1 (*FGFR2* fusions) (see Section 6.8.1 for further details).

Molecular pre-screening for *FGFR2* mutations/amplifications in Substudy 2 should be based on NGS testing (for details see Table 2 and Appendix 8) performed or commissioned by the respective study site.

If an eligible *FGFR2* GA status is either known or has been established (see Appendix 8), the patient may undergo clinical screening procedures. If the patient is still receiving prior systemic therapy, clinical screening procedures will be delayed until radiographically confirmed disease progression or intolerance to the ongoing systemic therapy is documented. After the study treatment eligibility is confirmed, patients will be enrolled and treated with continuous 300 mg QD of derazantinib capsules. A treatment cycle is defined as 28 days. Patients will receive treatment with derazantinib capsules until death, radiographic disease progression, unacceptable toxicity, or until another of the specified criteria is met for stopping therapy.

It is expected that most patients will receive between 1 and 8 months of treatment with derazantinib capsules. Dose delays and/or reductions will be allowed when derazantinib-related toxicity is observed (see Section 7.3 Dose Modifications). A related toxicity is defined as any toxicity considered related to derazantinib, i.e., definitively, probably, or possibly related, or when the relationship is unknown.

During the treatment period, patients will be evaluated every 2 weeks for the first cycle (Cycle 1 Days 1 and 15), and once every cycle thereafter (Day 1 of each cycle).

Tumor measurements will be done at Screening (within 28 days prior to the first dose of derazantinib), once every 8 weeks (two cycles) from the day of the first dose for the first six cycles and once every 12 weeks (three cycles) thereafter. For patients with PR or CR, the Investigator should perform a confirmation tumor measurement 4 to 5 weeks after the scan showing PR or CR. For patients with PD per Investigator assessment, a central radiology reviewer confirmation should be received prior to the patient's discontinuation from the study treatment if progression is seen on the first or second on-treatment scan. Patients who discontinue study drug for a reason other than radiographic disease progression, withdrawal of consent, death, or loss to follow-up should continue tumor evaluation visits if possible every 8–12 weeks until they start another anti-cancer therapy, experience disease progression, withdraw consent, die, or are lost to follow-up.

Pharmacodynamic assessments will include evaluation of tumor markers (CA19.9, CA125, CEA), biomarkers (FGF19, FGF21, FGF23), and cell-free circulating tumor deoxyribonucleic acid (ctDNA). Blood samples for tumor markers will be collected for all enrolled patients. Blood samples for biomarkers and ctDNA will be collected only from patients enrolled after completion of the interim analysis, and subject to the granting of appropriate regulatory and IRB/IEC approval. These blood samples will be collected on Day 1 of the first cycle, every 8 weeks (two cycles) for the first six cycles, once every 12 weeks (three cycles) thereafter, and at the End of Treatment visit. All collected samples will be evaluated in batches either during or at the end of the study.

Archival tumor samples will be obtained for all patients to enable additional molecular analyses with regard to the identified GAs and markers predictive of response at the laboratories selected by the Sponsor (see Section 6.8). In addition, further information on the molecular status of the tumor, including available full NGS reports may be collected.

To determine the PopPK parameters of derazantinib, blood samples will be collected on Day 1 and Day 15 of Cycle 1, and on Day 1 of Cycles 2, 3, and 4. Exploratory assessments of metabolites of derazantinib may also be investigated from these PK plasma samples.

All patients will be scheduled for sparse PK sampling. A subset of up to 20 patients (PK/biomarker subgroups) in each substudy will be asked to participate in rich PK sampling and/or urinary PK sampling (see Section 6.6).

HRQOL and symptom response will be measured using the QLQ-C30, QLQ-BIL21, and the EQ-5D. The G-SET/HTI is a single item, and will be used as an external anchor to determine the minimal important difference of the EQ-5D VAS, EORTC QLQ-C30, and QLQ-BIL21 scales (see Section 6.10 and Appendix 7).

Safety follow-up will be conducted at least 30 days after the administration of the last dose of study medication. Safety follow-up will include collection of AEs and changes in concomitant medication. Survival follow-up will start the day of the last dose of derazantinib; it will continue until the study has completed or other discontinuation criteria are met.

## 3.2 Rationale for study design

Intrahepatic cholangiocarcinoma is a rare malignancy and according to the Surveillance, Epidemiology, and End Results (SEER) data, between 1973 and 2012, the estimated incidence of iCCA increased from 0.44 to 1.18 cases per 100,000 person-years.

Molecular analysis of iCCA has identified *FGFR2* fusions and mutations as a potential drug target for FGFR inhibitors. *FGFR* mutations and fusions have been observed in 13.6% to 45% of iCCA. The documented fusions to date include: *FRGR2-TACC3*, *FGFR2-BICC1*, *FGFR2-AHCYL1*, *FGFR2-PPHLN1*, and *FGFR2-MGEA5* (Arai 2014, Borad 2014, Borad 2015, Graham 2014, Ross 2014, Sia 2015, Wu 2013).

Derazantinib, a potent pan-FGFR inhibitor, has shown anti-tumor effects in nonclinical studies on human tumors driven by oncogenic *FGFR* with an acceptable therapeutic window. In the Phase 1/2 clinical study, ARQ 087-101, derazantinib demonstrated early signs of clinical activity against malignancies with *FGFR* GAs, including iCCA harboring *FGFR2* fusions, mutations, or amplifications.

## 3.3 Study endpoints

### 3.3.1 Primary endpoints

**Substudy 1**

ORR was selected as the primary endpoint of this study. This endpoint is an acceptable surrogate endpoint of clinical benefit in this disease. ORR will be the proportion of patients with confirmed complete responses and partial responses by central radiology review as per RECIST version 1.1.

**Substudy 2**

PFS 3 will be the proportion of patients who have progression-free survival at 3 months from the first date of receiving study drug as assessed by survival status and central radiology review as per RECIST version 1.1.

### 3.3.2 Secondary efficacy endpoints

**Substudy 1 and Substudy 2**

- DoR will be calculated from the first date of documented tumor response to disease progression by central radiology review.
- PFS will be calculated from the first date of receiving study drug until radiographic disease progression by central radiology review or death
- OS will be calculated from the first date of receiving study drug until death.
- Changes in HRQOL and symptom response will be evaluated using the EORTC QLQ-C30, QLQ-BIL21, and EQ-5D VAS.

**Substudy 2**

- ORR will be the proportion of patients with confirmed complete responses and partial responses by central radiology review as per RECIST version 1.1.

### 3.3.3 Exploratory efficacy endpoints

- Changes in PD biomarkers from baseline to maximum change during the course of the treatment will be evaluated.
- ORR, PFS, OS, and DoR will be evaluated by PD biomarkers.
- Describe the proportion of patients with concordant molecular assessment from a liquid biopsy sample measuring GAs in circulating-cell free DNA compared to the DNA obtained from a tumor biopsy at baseline.
- TTP will be calculated based on central radiology review from the first date of receiving study drug or prior line of systemic therapy until radiographic disease progression)
  - TTP will be evaluated for derazantinib overall and by line of prior systemic therapy.
  - In addition, TTP will be assessed on the first and/or the last prior line of systemic therapy (reported) and will be compared to TTP on derazantinib
- The exposure-response relationship between derazantinib exposure and study measures of efficacy, toxicity and PD biomarkers will be analyzed.
- PopPK parameters of derazantinib will be evaluated (in addition, exploratory assessments of metabolites of derazantinib may also be investigated from the plasma PK samples)
- The percentage of administered derazantinib (and possibly its metabolites) over 24 h at steady-state may also be investigated.

### 3.3.4 Safety endpoint

Toxicities will be evaluated using NCI CTCAE version 4.03 criteria.

## 3.4 Study duration

The study is estimated to take approximately 4 years from First Patient First Visit to Last Patient Last Follow-up Visit. It is expected that most patients will receive between 1 and 8 months of treatment with derazantinib capsules.

Patients will receive treatment with derazantinib capsules until death, radiographic disease progression, unacceptable toxicity, or until another of the specified criteria is met for stopping therapy (see Section 5.7). Radiographic progressive disease must be confirmed by central radiology review prior to treatment discontinuation if progression is seen on the first or second on-treatment scan.

In Substudy 1, if the locally-documented (e.g., by NGS) *FGFR2* fusion positive status was tested and not confirmed by FISH by the central laboratory designated by the Sponsor after the commencement of study treatment, these patients will be assessed on a case-by-case basis (see Section 5.7.1).

Once a patient is discontinued from the study treatment, he/she and/or their family will be contacted for the long-term survival at least once every 3 months (± 2 weeks) until the study has completed or other discontinuation criteria are met (e.g., death, lost to follow-up, or withdrawal of consent for long-term [survival] follow-up).

For patients who demonstrate continued benefit (in Substudy 1 or Substudy 2) from receiving derazantinib at the time of study closure, the Sponsor aims to provide continued individual access to derazantinib, e.g., under a rollover study protocol, or in the context of compassionate use / named-patient access where applicable.

# 4 STUDY POPULATION SELECTION

## 4.1 Study population

This is a multi-center, open label, single arm study evaluating derazantinib in adult patients with inoperable or advanced iCCA and *FGFR2* fusions or *FGFR2* mutations or amplifications treated with at least one prior regimen of systemic therapy.

Patients' eligibility may be assessed in two steps: 1) pre-screening to assess the *FGFR2* GA status that will be followed by 2) clinical screening procedures.

Tissue samples for genetic testing will be obtained from patients who meet the following pre-screening eligibility criteria:

1. Signed written informed consent to permit tissue analysis.
2. 18 years of age or older.
3. No medical history that is excluded per the study treatment eligibility criteria (see Section 4.3).
4. ECOG performance status ≤ 1 (Appendix 2).
5. Eligible for or receiving systemic therapy for inoperable or advanced iCCA.
6. Not currently eligible for curative local or surgical therapy.

To be enrolled in the study, once the *FGFR2* GA status is determined, each prospective participant must meet all of the following inclusion criteria and none of the exclusion criteria.

## 4.2 Inclusion criteria

Each prospective study participant must meet ALL of the following inclusion criteria in order to be eligible for this study:

1. Signed written informed consent granted prior to initiation of any study-specific procedures.
2. 18 years of age or older.
3. Histologically or cytologically confirmed locally advanced, inoperable (where surgery is not indicated due to disease extension, co-morbidities, or other technical reasons), or metastatic iCCA or mixed histology tumors (combined hepatocellular-cholangiocarcinoma [cHCC-CCA]).
4. **Substudy 1**

   *FGFR2* fusion status based on the following assessments (see Section 6.8.1, Table 1):
   a) If central laboratory designated by the Sponsor:
      Positive FISH test; and/or
   b) If non-central laboratory:*
      i) Positive FISH or NGS test: patients may be enrolled and may start dosing, but central confirmation is required† (see Section 5.7.1).
      ii) Negative FISH or NGS test: tissue may be submitted to the central laboratory designated by the Sponsor, and patients may only be enrolled if the central test is positive.

   **Substudy 2**

   *FGFR2* mutation/amplification status (Appendix 8) based on NGS testing performed or commissioned by the respective study site (see Section 6.8.2, Table 2).

   *Note 1: If the FGFR2 mutation/amplification status is derived from plasma-based NGS testing, a tumor block or slides prepared thereof should be submitted for subsequent correlative tissue-based NGS testing at a laboratory identified by the Sponsor.*

   *Note 2: If the NGS test used cannot identify FGFR2 translocations, a FISH test is mandatory to confirm that none are present.*
5. Received at least one regimen of prior systemic therapy and then experienced documented radiographic progression (for Substudy 1), and have no satisfactory treatment alternatives (for Substudy 2).
6. Measurable disease by RECIST version 1.1 criteria.

* Using standard protocols and approved by local IRB/IEC, Clinical Laboratory Improvement Amendments (CLIA), or other similar agency. For enrollment of patients in the EU, assays must be fully CE-marked.

† The patient must not be enrolled if a negative FISH test is obtained from the central laboratory prior to commencing study treatment. Patients without central confirmation of an *FGFR2* fusion by the central FISH test will be assessed on a case-by-case basis (see Section 5.7.1).

7. ECOG performance status ≤ 1 (Appendix 2).
8. Adequate organ functions as indicated by the following laboratory values (based on screening visit values from the central laboratory).
   - Hematological
     - Hemoglobin (Hgb) ≥ 9.0 g/dL
     - Absolute neutrophil count (ANC) ≥ $1.5 \times 10^9$/L
     - Platelet count ≥ $75 \times 10^9$/L
     - International normalized ratio (INR) 0.8 to upper limit of normal (ULN) or ≤ 3 for patients receiving anticoagulant therapy such as warfarin or heparin
   - Hepatic
     - Total bilirubin ≤ 2 × ULN
     - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 ULN (≤ 5 × ULN for patients with liver metastases)
     - Albumin ≥ 2.8 g/dL
   - Renal
     - Serum creatinine ≤ 1.5 × ULN, or
     - Creatinine clearance of ≥ 30 mL/min as estimated by the Cockcroft-Gault equation
9. Female and male patients of child-producing potential must agree to avoid becoming pregnant or impregnating a partner, respectively, during the study*, and until at least 120 days after the last dose of derazantinib.

   Male patients are considered not to be of child-producing potential if they have azoospermia (whether due to vasectomy or an underlying medical condition). Female patients are considered not to be of child-producing potential if they are:
   - postmenopausal†, or
   - have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening, or
   - have a congenital or acquired condition that prevents childbearing.

   Male or female patients of child-producing potential must agree to comply with one of the following until at least 120 days after the last dose of derazantinib:

   a) Abstinence from heterosexual activity‡

* From the day of first study medication, or for oral contraception from 14 days before first study medication.

† Postmenopausal is defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post -menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is not sufficient.

‡ Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if it is employed during the entire period of risk associated with the study treatment and if it is considered highly effective by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not highly effective methods of contraception.

b) Using (or having their partner use) a highly effective method of contraception during heterosexual activity. Highly effective methods of contraception are*:
   - an intrauterine device (IUD)
   - vasectomy of a female patient's male partner
   - a contraceptive rod implanted into the skin
   - combined (estrogen- and progestogen-containing) or progestogen-only hormonal contraception associated with inhibition of ovulation (oral contraceptive pill [estrogen/progestin pill or progestin-only pill]contraceptive skin patch/implant, vaginal contraceptive ring, or subcutaneous contraceptive injection)

## 4.3 Exclusion criteria

Prospective study participants who meet ANY of the following criteria will not be eligible for enrollment into this study.

1. Receipt of treatment before the first dose of study drug (Cycle 1 Day 1) within an interval shorter than the following, as applicable:
   - One chemotherapy or biological (e.g., antibody) cycle interval
   - Five half-lives of any small-molecule investigational or licensed medicinal product
   - Two weeks, for any investigational medicinal product with an unknown half-life
   - Four weeks of curative radiotherapy
   - Seven days of palliative radiotherapy
   - 28 days of radiotherapy
2. Major surgery or locoregional therapy within 4 weeks of the first dose of derazantinib.
3. Previous treatment with any FGFR inhibitor (e.g., Balversa® [erdafitinib], Pemazyre® [pemigatinib], infigratinib, rogaratinib, futibatinib, lenvatinib**,** ponatinib, dovitinib, nintedanib, AZD4547, LY2784455).
4. Unable or unwilling to swallow the complete daily dose of derazantinib capsules
5. Clinically unstable central nervous system (CNS) metastases (to be eligible, patients must have stable disease ≥ 3 months, confirmed by magnetic resonance imaging (MRI) or computed tomography (CT) scan, and/or have CNS metastases well controlled by low-dose steroids, anti-epileptics, or other symptom-relieving medications)
6. Current evidence of clinically-significant corneal or retinal disorder likely to increase the risk of eye toxicity, including but not limited to bullous/band keratopathy, keratoconjunctivitis (unless keratoconjunctivitis sicca), corneal abrasion, inflammation/ulceration, confirmed by ophthalmologic examination

* If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as a highly effecive method of contraception for subjects participating at sites in this country/region.

7. Concurrent uncontrolled or active hepatobiliary disorders, untreated or ongoing complications after laparoscopic procedures or stent placement, including but not limited to active cholangitis, biloma or abscess (to be eligible, the patients have to be treated and disorders/complications should be resolved within 2 weeks prior to the first dose of derazantinib)
8. History of significant cardiac disorders:
   - Myocardial infarction (MI) or congestive heart failure defined as Class II to IV per the New York Heart Association (NYHA) classification within 6 months of the first dose of derazantinib (MI that occurred > 6 months prior to the first dose of derazantinib are permitted)
   - QTcF > 450 msec for men and QTcF > 460 msec for women
9. Serum electrolyte abnormalities defined as follows:
   - Hyperphosphatemia: serum phosphate > institutional ULN
   - Hyperkalemia: serum potassium > institutional ULN
   - Hypokalemia: serum potassium < institutional LLN
   - Hypercalcemia: corrected serum calcium > 3.1 mmol/L (> 12.5 mg/dL)
   - Hypocalcemia: corrected serum calcium < 1.75 mmol/L (< 7.0 mg/dL)
   - Hypomagnesemia: < 0.4 mmol/L (< 0.9 mg/dL)
10. Significant gastrointestinal disorder(s) that could, in the opinion of the Investigator, interfere with the absorption, metabolism, or excretion of derazantinib (e.g., Crohn's disease, ulcerative colitis, extensive gastric resection)
11. History of additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, and *in situ* cervical cancer.
12. Concurrent uncontrolled illness not related to cancer, including but not limited to:
   - Psychiatric illness/substance abuse/social situation that would limit compliance with study requirements
   - Known uncontrolled human immunodeficiency virus (HIV) infection
   - Severe bacterial, fungal, viral and/or parasitic infections under treatment with therapeutic oral or IV medication at the time of first dose of study drug administration
13. Blood or albumin transfusion within 5 days of the blood draw being used to confirm eligibility
14. Pregnant or breast feeding
15. Known hypersensitivity to derazantinib, or to any of the study drug excipients (starch, lactose, crospovidone, magnesium stearate).

## 4.4 Number of patients

In Substudy 1, approximately 100 patients who meet all eligibility criteria will be enrolled and treated with 300 mg QD orally of derazantinib capsules. In order to evaluate 100 patients for efficacy, it is anticipated that over 1,000 patients will be tested for the presence of *FGFR2* fusions.

In Substudy 2, up to approximately 43 mITT-evaluable patients (approximately 15 patients in Stage 1, and an additional 28 patients if the study proceeds to Stage 2) with iCCA and an *FGFR2* mutation or amplification who meet the study entry criteria will receive oral derazantinib capsules 300 mg QD. To evaluate 43 patients for efficacy, it is anticipated that more than 800 patients will be tested for the presence of an *FGFR2* mutation or amplification.

# 5 STUDY TREATMENTS

Before the start of any study required procedures, including forwarding any tissue sample for analysis, the Investigator or designee must obtain a signed written informed consent form (ICF) for the study from each prospective study participant or his/her legal representative. The Investigator or designee must confirm that the patient has documented iCCA.

In Substudy 1, the patient must test positive for *FGFR2* fusion by the central laboratory designated by the Sponsor, or have documented *FGFR2* fusion based on testing conducted at a local or central laboratory approved by local IRB/IEC, by CLIA or other similar agency. **For enrollment of patients in the EU, commercially-used assays must be either fully CE-marked or CE-marked for analytical performance; tests manufactured by health institutions and used only on their own patients are exempt from the Medical Devices Regulation requirements, and do not have to be CE-marked.**

If a patient has documentation from the central laboratory indicating that they test negative for *FGFR2* fusion, that patient may not be enrolled in the study. If *FGFR2* fusion is identified by a laboratory other than the Sponsor's central laboratory, then archival and/or recent tissue biopsy samples must be collected for further confirmatory testing by FISH by the Sponsor's central laboratory. Tissue from patients with a negative test based on local testing may be submitted to central confirmatory FISH testing. If central FISH testing is positive, then the patient may be enrolled in the study.

In Substudy 2, the patient must test positive for *FGFR2* mutations/amplifications and negative for any concurrent *FGFR2* translocations (see Appendix 8) by NGS testing using standard protocols (see Section 6.8.2, Table 2)**.**

Study visits will consist of a Pre-screening visit, if *FGFR2* fusion and mutation/amplification status is unknown, and/or a Screening visit, during which the patient's eligibility for the study and baseline disease status will be evaluated. Following the first dose of derazantinib capsules, patients will be evaluated every 2 weeks for the first cycle (Cycle 1 Days 1 and 15), and once every 4 weeks (Day 1 of each subsequent cycle) thereafter. A cycle is defined as 28 days/4 weeks.

Additionally, an End of Treatment visit, 30-day Safety Follow-up visit, and Survival Follow-up(s) will be performed (see Appendix 1 for the Schedule of Assessments).

Following the Screening evaluation, and a determination by the Investigator and the Sponsor's Medical Monitor that the patient meets all eligibility criteria, the patient will be enrolled.

## 5.1 Informed consent

Sample ICFs with core information will be provided to each study site. Prior to study initiation at a given study site, each site/Investigator must obtain a written approval/favorable opinion from its respective IRB/IEC for the ICF and any other written information to be provided to patients. All ICFs must be compliant with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and local regulations, and must be approved by the Sponsor prior to submission to the IRB/IEC. The written approval of the IRB/IEC, together with the approved patient information/ICF, must be maintained in the study master files.

Written informed consent must be obtained from a prospective study participant before any study-specific procedures are performed on that individual, including forwarding any tissue sample for analysis. Patients who agree to participate in the study will sign the most recently approved ICF and will be provided with a copy of the fully executed document. The ICF can be signed greater than 28 days prior to dosing, and does not need to be re-signed prior to dosing unless specific reasons apply (e.g., a new approved consent version has been issued). The original, fully executed ICF will be maintained in the respective patient's clinical study file.

## 5.2 Pre-screening visit

After written informed consent is obtained, patients will be pre-screened prior to enrollment in the study. The objective of the pre-screening is to assess the patient's *FGFR2* fusion and mutation/amplification status.

- Pre-screening for *FGFR2* fusions in Substudy 1 may be based on local or central testing. If pre-screening is performed based on a local test, then a central confirmation by the *FGFR2* break-apart FISH Probe Kit test is required for Substudy 1 (see Section 6.8.1 for further details).
- Pre-screening for *FGFR2* gene mutations or amplifications in Substudy 2 will be performed based on NGS testing of tissue or plasma samples (see Section 6.8.2 for further details).
- Patients with known eligible *FGFR2* GA status and no requirement for central confirmation (Substudy 1 only) may undergo clinical screening procedures after after written informed consent is obtained.

For genetic testing, blood samples or tumor tissue from either a fresh biopsy or an archival tumor block should be subjected to molecular testing only from patients who meet the following pre-screening eligibility criteria:

1. Signed, written informed consent to permit tissue analysis
2. 18 years of age or older
3. No medical history that is excluded per the study treatment eligibility criteria (see Section 4.3)
4. ECOG performance status ≤ 1 (see Appendix 2)
5. Eligible for or receiving systemic therapy for inoperable or advanced iCCA
6. Not currently eligible for curative local or surgical therapy

## 5.3 Screening evaluation

After an eligible *FGFR2* fusion or *FGFR2* mutation/amplification status is confirmed, the patient's further eligibility for the study and baseline disease status will be assessed. The following will be evaluated and documented within 28 days prior to the first dose of derazantinib:

- Medical history (see Section 6.1).
- Record prior and concomitant medications (medications used within 30 days prior to the first dose of derazantinib).
- Tumor imaging assessments, according to RECIST 1.1 (see Section 6.9 and Appendix 6). Note: imaging assessments can be used as a Baseline assessment if they were performed within 28 days prior to the first dose of derazantinib.
- Physical examination (see Section 6.2).
- Vital signs (height, weight, temperature, blood pressure, respiration rate, and pulse).
- ECOG performance status (see Appendix 2).
- Complete opthalmological examination (see Section 6.3).
- Clinical blood tests (see Section 6.5).
- Serum pregnancy test, if applicable, within 72 hours prior to dosing (see Inclusion criterion 9, Section 6.5, and Section 8.8.2).
- 12-lead ECG (see Section 6.4).

Patients who satisfy all of the inclusion criteria and none of the exclusion criteria may be enrolled in the study.

Also, in order to better understand the disease, for all patients with confirmed FGFR2 fusion status or gene mutation/amplification, detailed records of prior systemic treatments and responses will be collected in the electronic data capture (EDC) system. In addition, all eligible (enrolled and dosed) patients will be asked to permit their CT/MRI scans performed during prior therapy(ies) to be submitted to the central imaging laboratory.

## 5.4 Treatment visits

Enrolled patients will be evaluated on Day 1 and Day 15 of Cycle 1 and on Day 1 of every cycle thereafter. All visits are based on the date of the first dose at Cycle 1 Day 1 regardless of drug holds. If a patient visit deviates from the protocol permitted window, the next visit must be done at the correct time based on the date of Cycle 1 Day 1.

### 5.4.1 Cycle 1, Day 1

The following assessments will be made during this visit (all assessments except for AE assessment, 12-lead ECG, and post-dose PK blood collection must be performed prior to the first dose):

- EORTC QLQ-C30 and QLQ-BIL21, and EQ-5D, questionnaires (should be completed by the patient prior to being evaluated by the physician) (see Section 6.10 and Appendix 7)
- Physical examination (see Section 6.2)
- Vital signs (weight, temperature, blood pressure, respiration rate, and pulse)
- ECOG performance status (see Appendix 2)
- Clinical blood tests (see Section 6.5)
- Serum or urine pregnancy test, if applicable (see Section 6.5, and Section 8.8.2)
- Blood samples for PK (see Section 6.6 and Appendix 3)
- Blood samples for tumor markers (see Section 6.7 and Appendix 3)
- Blood samples for biomarkers and ctDNA will be collected only from patients enrolled after completion of the interim analysis, and subject to the granting of appropriate regulatory and IRB/IEC approval (see Section 6.7 and Appendix 3)
- 12-lead ECGs (performed pre-dose and 6–8 hours after the first dose) (see Section 6.4)
- Record concomitant medications
- Dispense and administer derazantinib capsules
- Assess AEs after derazantinib administration

### 5.4.2 Cycle 1, Day 15 (± 3 days)

The following assessments will be made during this visit:

- Physical examination (see Section 6.2)
- Vital signs (weight, temperature, blood pressure, respiration rate, and pulse)
- ECOG performance status (see Appendix 2)
- Clinical blood tests (see Section 6.5)
- Blood samples for PK (see Section 6.6 and Appendix 3)
- 12-lead ECGs (performed pre-dose and 6–8 hours after the daily dose) (see Section 6.4)
- Assess AEs, including any potential eye toxicity*
- Record concomitant medications

* Patients who develop ocular symptoms or changes in visual acuity while on the study should be referred to an ophthalmologist for a complete eye examination.

### 5.4.3 Cycle 2+, Day 1 (± 3 days)

The following assessments will be made during this visit:

- EORTC QLQ-C30 and QLQ-BIL21, and EQ-5D, questionnaires (should be completed by the patient prior to being evaluated by the physician) every 8 weeks (two cycles) for the first six cycles (on C3D1, C5D1, C7D1) and once every 12 weeks (three cycles) thereafter (on C10D1, C13D1, etc.) The G-SET/HTI should be additionally completed by the patient after 8 weeks (at Cycle 3 Day 1) and 16 weeks (at Cycle 5 Day 1) (see Section 6.10 and Appendix 7).
- Physical examination (see Section 6.2)
- Complete opthalmological examination at C2D1, C3D1, C4D1, and C5D1 only, and if clinically indicated thereafter; see Section 6.3)
- Vital signs (weight, temperature, blood pressure, respiration rate, and pulse)
- ECOG performance status (see Appendix 2)
- Clinical blood tests (see Section 6.5)
- Serum or urine pregnancy test, if applicable (see Section 6.5, and Section 8.8.2)
- Blood samples for tumor markers, biomarkers, and ctDNA every 8 weeks (two cycles) for the first 6 cycles (on C3D1, C5D1, C7D1) and once every 12 weeks (three cycles) thereafter (on C10D1, C13D1, etc.) (see Section 6.7 and Appendix 3). Note: Blood samples for biomarkers and ctDNA will be collected only from patients enrolled after completion of the interim analysis, and subject to the granting of appropriate regulatory and IRB/IEC approval (see Section 6.7 and Appendix 3)
- Blood samples for PK (Day 1 of Cycles 2, 3, and 4) (see Section 6.6 and Appendix 3)
- Urine sample for PK (Day 1 of Cycle 2 only), starting on an empty bladder before daily dose administration and until 24 h after dosing (immediately prior to the next dose) (see Appendix 3)
- CT/MRI (chest, abdomen, and pelvis) tumor measurement and staging every 8 weeks (two cycles) for the first six cycles (on C3D1, C5D1, C7D1) and once every 12 weeks (three cycles) thereafter (on C10D1, C13D1, etc.) (see Section 6.9 and Appendix 6)
- 12-lead ECG. Additional ECG(s) may be conducted if clinically indicated (see Section 6.4)
- Assess AEs, including any potential eye toxicity*
- Record concomitant medications
- Dispense derazantinib capsules and perform drug accountability of returned drug. Note: To avoid unnecessary waste of study drug, in cases where treatment was interrupted and/or dose was reduced, the patient can continue dosing from the previously dispensed bottle until the next drug dispensing visit where re-supply is needed to maintain the protocol dosing regimen.

* Patients who develop ocular symptoms or changes in visual acuity while on the study should be referred to an ophthalmologist for a complete eye examination.

### 5.4.4 End of Treatment visit

The following assessments will be made during the End of Treatment visit (+ 7 days from the date of the last dose administration or after the decision to permanently discontinue dosing was made):

- EORTC QLQ-C30 and QLQ-BIL21, and EQ-5D, questionnaires (should be completed by the patient prior to being evaluated by the physician) (see Section 6.10 and Appendix 7)
- Physical examination (see Section 6.2)
- Complete opthalmological examination (see Section 6.3)
- Vital signs (weight, temperature, blood pressure, respiration rate, and pulse)
- ECOG performance status (see Appendix 2)
- Clinical blood tests (see Section 6.5)
- Serum pregnancy test, if applicable (see Section 6.5, and Section 8.8.2)
- 12-lead ECG (see Section 6.4)
- Blood samples for tumor markers (see Section 6.7 and Appendix 3)
- Blood samples for biomarkers and ctDNA will be collected only from patients enrolled after completion of the interim analysis, and subject to the granting of appropriate regulatory and IRB/IEC approval
- CT/MRI (chest, abdomen, and pelvis) tumor measurement and staging if the prior scan was not done within four weeks (28 days) prior to this visit or if the prior scan did not show radiographic disease progression (see Section 6.9 and Appendix 6)
- Assess AEs, including any potential eye toxicity*
- Record concomitant medications
- Perform drug accountability of returned drug

## 5.5 30-day Safety Follow-up visit

All patients will be followed for a minimum of 30 days after the last dose of derazantinib. During the 30-day safety follow-up period, AEs and changes in concomitant medication should be reported.

Patients with unresolved study drug-related AEs (occurred during the study treatment period or the 30-day safety follow-up period) will be followed until, in the opinion of the Investigator, study drug related toxicities have resolved to baseline, CTCAE Grade 1, stabilized, or are deemed to be irreversible. A study drug-related AE is defined as an AE that is definitely, probably, or possibly related to the treatment with derazantinib, or when the relationship is unknown. If a patient receives other anti-cancer therapy within the 30-day safety follow-up period, the follow-up for AEs will cease, beginning the first day of the new therapy.

* Patients who develop ocular symptoms or changes in visual acuity while on the study should be referred to an ophthalmologist for a complete eye examination.

In addition, at the 30-day Safety Follow-up visit, the following assessments will be made:

- EORTC QLQ-C30 and QLQ-BIL21, and EQ-5D, questionnaires (should be completed by the patient prior to being evaluated by the physician) (see Section 6.10 and Appendix 7)
- Physical examination (see Section 6.2)
- Complete opthalmological examination (see Section 6.3)
- Vital signs (weight, temperature, blood pressure, respiration rate, and pulse)
- ECOG performance status (see Appendix 2)
- Clinical blood tests (see Section 6.5)
- Serum- or urine pregnancy testing (to be performed monthly until 120 days after the last administration of study drug) (see Section 8.8.2)

## 5.6 Survival Follow-up (at least every 3 months ± 14 days)

Patients will be followed for survival from the day of the last dose of derazantinib. All patients and/or family will be contacted at 3-month intervals (± 14 days) and record the patient status as Alive (date); Dead (date); Alive, but withdrew consent for further follow-up; Lost to Follow Up. Survival updates may be made more often than every 3 months if the patient is seen at the investigational site for other reasons and for study level survival sweep(s). Survival follow-up will continue until the study has completed or other discontinuation criteria are met.

Note: Survival follow-up can be done either as an office visit, over the telephone, or by collection of public records in accordance with local laws.

## 5.7 Discontinuation from the treatment or study

### 5.7.1 Patient discontinuation from treatment

Patients will be removed from the study treatment at any time if they meet any of the following criteria:

- Documented radiographic progression of disease
  - Radiographic progression must be confirmed by central radiology prior to treatment discontinuation if progression is seen on the first or second post-treatment scan
  - Patients may remain on study treatment if, in the opinion of the Investigator and with the agreement of the Medical Monitor, they continue to derive benefit from derazantinib

- Central negative or unconfirmed FISH test result for an *FGFR2* fusion in patients enrolled based on a locally-documented *FGFR2* fusion positive
  - If the central FISH test could not be performed for technical reasons and the patient did not experience radiographic progression, the patient may be allowed to continue the study treatment
  - If the central FISH test result is negative for an *FGFR2* fusion, the patient should be discontinued from the study treatment, other than in exceptional cases when, based on ethical considerations and an individual benefit-risk assessment, discontinuation of the patient from the study treatment is considered unacceptable
- Documented clinical progression of disease
- Clinical unacceptable toxicities despite optimal treatment or dose reduction
- Pregnancy (see Section 8.8.2).
- Patient decision to discontinue treatment and study visits
- Withdrawal of consent from treatment and study follow up calls
- Non-compliance with any part of the study, as assessed by the Investigator or Medical Monitor
- Investigator's decision after discussion with the Medical Monitor or designee
- Death

### 5.7.2 Patient discontinuation from the study

Patients who discontinue from study treatment will still be followed for survival either through direct contact or collection of public records (e.g., death certificate) in accordance with local laws, unless they meet any of the following criteria:

- Withdrawal of consent for long-term (survival) follow-up
- Lost to follow-up
- Death

## 5.8 Study discontinuation

The Sponsor reserves the right to temporarily or permanently discontinue the study at any site or at any time. Reasons for study discontinuation may include, but are not limited to, the following:

- Safety concerns
- Poor enrollment
- Non-compliance with the protocol, GCP guidelines, or other regulatory requirements by the Investigator(s)
- Request to discontinue the study by a regulatory or health authority
- Discontinuation of product development
- Manufacturing difficulties/concerns

The Sponsor and/or designee will promptly inform all Investigators and the appropriate regulatory authorities if the study is suspended or terminated for safety reasons. In the event of such a study termination, the Investigator must notify the IRB or IEC, as appropriate.

# 6 STUDY PROCEDURES

## 6.1 Medical history and prior/concomitant medications

Medical history will include but not be limited to the following:

- Demography: year of birth, gender, race (unless local regulations do not permit), ethnicity (US patients)
- Clinically significant prior diagnoses, surgeries, and current medications
  - Medications used within 30 days prior to the first dose of derazantinib and throughout the treatment period should be reported
- Prior cancer history, current cancer diagnosis, tumor stage at the time of diagnosis and screening, previous anti-cancer therapy including dates, duration and outcome of treatment, previous radiation therapy including anatomic site, dose and dates of treatment, previous cancer-related surgical procedures, including type of the procedure and dates.
  - For all patients with confirmed *FGFR2* GAs eligible for the study (i.e., either *FGFR2* fusions, or mutations/amplifications listed in Appendix 8), detailed records of prior systemic treatments and responses will be collected in the EDC system;
  - All eligible (enrolled and dosed) patients will be asked to forward CT/MRI scans performed during prior therapy(ies) to the central imaging laboratory.

## 6.2 Physical examination and ECOG performance status

Complete physical examination of the major body systems (Screening visit, Cycle 1 Days 1 and 15, Day 1 of all subsequent cycles, End of Treatment visit, and 30-day Safety Follow-up visit), height (Screening visit only), weight, vital signs (temperature [oral, axillary, or tympanic], blood pressurte, respiration rate, and pulse), and ECOG Performance Status (Appendix 2). ECOG performance status will also be evaluated during the Pre-Screening visit.

## 6.3 Complete ophthalmological examination

A complete opthalmological examination should be administered by an ophthalmologist at the Screening visit, for the first four cycles (i.e., Day 1 of Cycles 2–5), at the End of Treatment visit, at the 30-day Safety Follow-up visit, and if clinically indicated. The complete eye examination may include the following:

- visual acuity
- tonometry
- anterior segment evaluation
- retinal evaluation, which may include tests such as fluorescein angiography and optical coherence tomography

For the individual patient, the same methods of assessment should be used throughout the study.

During the study, per Investigator's discretion, a routine opthalmological examination may be performed.

Patients who develop ocular symptoms or changes in visual acuity while on the study should be referred to the ophthalmologist for a complete opthalmological examination.

## 6.4 12-lead electrocardiogram

A standard, triplicate, 12-lead ECG must be performed using the pre-programmed device provided by the Sponsor:

- at the Screening visit
- on Day 1 and Day 15 of Cycle 1 (pre-dose, and approximately 6–8 hours after the dosing)
- on Day 1 of Cycle 2 (pre-dose)
- on Day 1 of Cycle 3 (pre-dose, and approximately 6–8 hours after the dosing)
- on Day 1 of Cycle 4 and all subsequent cycles (pre-dose); and
- at the End of Treatment visit

Measurements should be separated by ~1 min and be taken within a 5 min time window. The on-treatment ECGs should be performed as close as possible to the corresponding PK blood collection time point during those visits; if possible, ECG should be measured first, and then blood collected for PK within 5–10 minutes. Additional ECGs may be conducted if clinically indicated.

ECGs must always be recorded after at least 5 min rest and while the patient is in a supine or semi-supine position. ECGs must be assessed, and the printouts signed and dated, by the Investigator or his/her designee.

All ECGs are to be transmitted to a central ECG laboratory for evaluation, including QTc assessment.

## 6.5 Clinical laboratory tests

Safety laboratory determinations will include hematology, blood chemistry, liver function tests, and coagulation tests at the Screening visit (within 1 week prior to dosing), Cycle 1 Days 1 and 15, Day 1 of all subsequent cycles, the End of Treatment visit, and the 30-day Safety Follow-up visit. If clinically indicated, some or all of these tests may be repeated on other study days. All laboratory tests will be performed at a central laboratory designated by the Sponsor.

- Hematology: complete blood count (CBC) including hemoglobin, hematocrit, white blood cell count (WBC) with 5-part differential, red blood cell (RBC) count, and platelet count
- Blood chemistry: albumin, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, magnesium, phosphate, potassium, total protein, sodium, and uric acid
  - Creatinine clearance as calculated by the Cockcroft-Gault equation (at the Screening visit only)
  - 25-hydroxy vitamin D and 1,25-dihydroxy vitamin D (at C1D1, C3D1, C5D1, and the End of Treatment visit only),

- Liver function tests (LFT): ALT, AST, ALP, total and direct bilirubin, lactate dehydrogenase (LDH)
- Coagulation tests: prothrombin time (PT), INR, and partial prothrombin time (PTT) (at the Screening and End of Treatment visits and if clinically indicated)
- Serum pregnancy test: for women of child-producing potential at the Screening visit (within 72 hours prior to dosing), and End of Treatment visit. In addition, serum- or urine pregnancy testing will be performed monthly (on Day 1 of each treatment cycle) while the patient receives study treatment, at the 30-day Safety Follow-up visit, and monthly until 120 days after the last administration of study drug. Pregnancy testing after the End of Treatment may be performed at the patient's local gynecologist to reduce the burden related to study visits at the site, but must be communicated to the study investigator.

## 6.6 Pharmacokinetic assessments

Blood samples will be taken to determine the PopPK parameters of derazantinib. Exploratory assessments of metabolites of derazantinib may also be investigated from the same samples.

Time windows are allowed for sample collection as detailed in Appendix 3.

### 6.6.1 Sparse PK sampling (all patients)

On Cycle 1 Day 1 and Day 15, and on Cycle 3 Day 1, PK plasma samples will be collected pre-dose and between 6 and 8 hours after the daily dose of derazantinib. On Day 1 of Cycles 2 and 4, PK plasma samples will be collected at pre-dose (see Appendix 3). The blood sampling date and time and the time of derazantinib administration on the day of the PK blood draw and on the day prior to the PK blood draw should be recorded on the electronic case report form (eCRF).

### 6.6.2 Rich PK sampling (additional consent required)

In the PK/biomarker subgroup (up to 20 patients), on Day 1 of Cycle 1 and Cycle 2, serial PK plasma samples will be collected pre-dose, and 1, 2, 4, 6, 8, 10, 12, and 24 h after the daily dose of derazantinib (immediately prior to the next dose); the 10 and 12 h time-points are optional. On Day 15 of Cycle 1 and Day 1 of Cycle 3, PK plasma samples will be collected pre-dose and between 6 and 8 hours after the daily dose of derazantinib. On Day 1 of Cycle 4, PK plasma samples will be collected at pre-dose (see Appendix 3). Patients will be asked for an additional consent to participate in these assessments.

### 6.6.3 Urinary PK sampling (additional consent required)

Patients who undergo urinary PK sampling should also undergo rich blood PK sampling. In the PK/biomarker subgroup (up to 20 patients), urine will be collected over a 24 h interval on Day 1 of Cycle 2 to determine renal excretion of derazantinib. Exploratory assessments of metabolites of derazantinib may also be investigated from the PK urine samples (see Appendix 3). Patients will be asked for an additional consent to participate in these assessments.

## 6.7 Pharmacodynamic assessments

The goal of PD assessments is to identify additional markers to allow a better prediction of response to derazantinib or other cancer treatments, and to evaluate the tumoral and serum- or plasma-based PD response in patients treated with derazantinib.

Blood samples for PD assessments will be collected for serum tumor markers (CA19.9, CA125, CEA), biomarkers (FGF19, FGF21, FGF23), and ctDNA prior to the first dose on Day 1 of Cycle 1, and on Day 1 of every 8 weeks (every two cycles) for the first six cycles (C3D1, C5D1, C7D1), once every 12 weeks (three cycles) thereafter (C10D1, C13D1, etc.), and at the End of Treatment visit. Blood samples for serum tumor markers will be collected for all enrolled patients. Blood samples for biomarkers and ctDNA will be collected only from patients enrolled after completion of the interim analysis.

Archival tumor samples will be obtained for all patients to enable additional molecular analyses with regard to the identified GAs and markers predictive of response at the laboratories selected by the Sponsor (see Section 6.8).

The planned analyses include, but are not limited to, biomarkers identifying additional markers to allow a better prediction of response to derazantinib or other cancer treatments, biomarkers representing further MAPK (RAS/RAF/MEK/ERK), PI3K/AKT, and JAK/STAT pathways, biomarkers indicating PI3K, PTEN, EGFR, MET and ERB3 signaling, and biomarkers demonstrating phosphorylation status of phospho-S6, phosphor-STAT, phospho-AKT, phospho-MEK, phospho-ERK, and RNA-expression of proteins activated by the MAPK-pathway, such as SPRY2 and DUSP6.

All collected samples will be evaluated in batches either during or after the end of the study. All testing will be performed at a laboratory designated by the Sponsor. Samples remaining from PD analyses may be used to supplement diagnostic analysis batches, and vice versa.

## 6.8 Tumor tissue testing for confirmation of patient eligibility

To be eligible for enrollment, the patient must either test positive for *FGFR2* fusion (Substudy 1), or test positive for *FGFR2* mutation/amplification (Substudy 2).

### 6.8.1 FISH testing

FISH testing will be the primary method to confirm *FGFR2* fusions in Substudy 1.

If the *FGFR2* fusion is identified by a laboratory other than the Sponsor's central laboratory, then archival and/or recent tissue biopsy samples or a tissue block suitable for biomarker analysis must be available for confirmatory testing using the break-apart FISH test by the Sponsor's central laboratory (ARUP laboratories; Salt Lake City, USA). These samples should be sent to the central laboratory as early as possible, and no later than 4 weeks after the patient received the first dose of derazantinib.

Table 1 describes the testing approach depending on *FGFR2* GA status and available results from local molecular pre-screening. Central laboratory FISH testing using the break-apart FISH test should be performed on all tissue samples from potentially eligible patients with iCCA for whom:

- No local pre-screening results (by FISH or NGS) are available, or
- Where pre-screening results (by FISH or NGS) have identified an *FGFR2* fusion and the patient is planned for study inclusion or has already been included in the study

Tissue from Substudy 1 patients with a negative result from a test other than the central laboratory FISH test designated by the Sponsor may also be submitted to central confirmatory FISH testing. If the central FISH testing is positive, the patient may be enrolled in the study.

**Table 1 Substudy 1: Overview of genetic testing for *FGFR2* fusions**

| Local pre-screening result | Confirmatory testing approach | Main testing purpose/comment |
|---|---|---|
| No local testing performed | Central FISH (mandatory) | Detect eligible *FGFR2* fusion status |
| Local FISH test positive for *FGFR2* fusion | Central FISH (mandatory) | Confirm or exclude *FGFR2* fusion |
| | NGS (optional) | Characterize *FGFR2* fusion |
| Local NGS test positive for *FGFR2* fusion | Central FISH (mandatory) | Confirm *FGFR2* fusion |
| Local NGS test negative for *FGFR2* fusion | Central FISH (optional, depending on tissue availability) | Detect eligible *FGFR2* fusion status |

**Tumor tissue requirements:**
Central FISH: ≥ 6 consecutive, unstained, 5 ± 1 µm thick sections placed on positively charged slides.
NGS testing: ≥ 10 consecutive, unstained, 5 ± 1 µm thick sections placed on positively charged slides, and one H&E slide.

Central FISH testing will be performed on formalin-fixed paraffin-embedded (FFPE) primary liver cancer specimens, including iCCA tissue samples. A minimum of 6 consecutive, unstained, 5 ± 1 µm thick sections placed on positively charged slides are required. Archived tissue specimens may be submitted if they meet the requirements outlined in the Laboratory Manual.

Archival tumor samples will be obtained for all patients to enable additional molecular analyses with regard to the identified GAs and markers predictive of response at the laboratories selected by the Sponsor.

### 6.8.2 NGS testing

NGS testing will be the primary method to establish a tumor's *FGFR2* mutation/ amplification status in Substudy 2; any level of *FGFR2* gene amplification will be eligible. Patients with an eligible *FGFR2* mutation/amplification will not be eligible for clinical screening if the tumor concurrently harbors any *FGFR2* translocation. Table 2 describes the testing approach depending on *FGFR2* GA status and available results from local molecular pre-screening.

NGS testing may also be used to detect and characterize *FGFR2* fusions in Substudy 1, provided tumor tissue is submitted for the mandatory confirmatory FISH test (see Section 6.8.1).

Usually, NGS testing results will already be available for patients based on prior testing in the context of standard of care for the patient, or will be performed at the study site or commissioned at facilities of commercial providers.

If required to comprehensively determine the eligible *FGFR2* GA status, NGS testing may be complemented by validated/approved other molecular tests. Tumor samples may be analyzed at other laboratories identified by the Sponsor to further characterize the identified GAs and molecular markers predictive of response.

**Table 2 Substudy 2: Overview of genetic testing for *FGFR2* mutations/amplifications**

| Local pre-screening result | Confirmatory testing approach | Main testing purpose/comment |
|---|---|---|
| No local testing performed | Mandatory: Validated/approved NGS test* (FFPE tissue samples).<br>Additional FISH testing is ONLY mandatory if *FGFR2* translocations cannot be detected by the applied NGS test. | Detect eligible *FGFR2* mutation/amplification status.<br>Exclude any concurrent *FGFR2* translocations. |
| Local tissue- or plasma-based NGS test* positive for *FGFR2* mutation/amplification | Additional FISH testing is ONLY mandatory if *FGFR2* translocations cannot be detected by the applied NGS test. | Exclude any concurrent *FGFR2* translocations. |
| Local tissue-based NGS test* negative for *FGFR2* mutation | Optional: Use different validated/ approved NGS assay.*<br>Additional FISH testing is ONLY mandatory if *FGFR2* translocations cannot be detected by the applied NGS test. | Confirm presence of *FGFR2* mutation/amplification.<br>Exclude any concurrent *FGFR2* translocations. |

**Tumor tissue for additional correlative analyses should be submitted from all patients enrolled in the study; tumor tissue requirements:**

NGS testing: ≥ 10 consecutive, unstained, 5 ± 1 µm thick sections placed on positively charged slides, and one H&E slide.

Central FISH: ≥ 6 consecutive, unstained, 5 ± 1 µm thick sections placed on positively charged slides.

* For enrollment of patients in the EU, assays must be either fully CE-marked or CE-marked for analytical performance, unless such assays are exempt from this requirement by the IVDD (*Directive 98/79/EC*), i.e., manufactured and appropriately validated within health-institution laboratories for use in that environment and not subject to commercial transactions.

For enrollment of patients outside of the EU, assays must use standard protocols approved by the local IRB/IEC, CLIA, or other similar agency, or, where applicable, US FDA-approved fully CE-marked industrial scale assays.

The Sponsor will review and confirm the appropriateness of the NGS testing approach for each study site, and will reimburse costs for NGS testing as appropriate, unless the NGS testing is already available for a patient in the context of prior standard of care testing.

For Substudy 2, available liquid biopsy findings from NGS testing from contemporary liquid biopsies may be used to determine the patient's *FGFR2* molecular status (Table 2); however, a tumor block or slides prepared thereof should be submitted for correlative tissue-based NGS testing at a laboratory identified by the Sponsor. De novo NGS testing should be performed on tumor tissue samples from potentially eligible patients with iCCA for whom no local molecular pre-screening results are available (Table 2).If possible, NGS testing should be performed on formalin-fixed paraffin-embedded (FFPE) primary liver cancer specimens; alternatively, tissue samples of different organ origin may be used if in accordance with the assay's specifications. Archived tissue specimens may be submitted (for minimum tissue requirements, see Table 2) if they meet the requirements outlined in the Laboratory Manual. Detailed instructions for collection, shipment, and testing of blood and tissue samples for PK and PD assessments will be provided in the Laboratory Manual.

NOTE: Samples for PK, and PD assessments will be labeled by personnel from the institution with the patients' study ID; patients' identity will not be made known to employees from the Sponsor, additional collaborators, or other investigators. Samples will only be used for the purposes of the protocol and will only be used by the Sponsor's personnel or by an external laboratory chosen by the Sponsor to outsource the analyses according to internal guidelines. Samples will be kept until all protocol-related analyses are completed, for a period not exceeding 10 years or as required by local law.

## 6.9 Tumor imaging assessments

Baseline tumor imaging assessments must be done at the time of the Screening visit. However, if an assessment has been performed for routine clinical management prior to obtaining informed consent after administration of the last dose of any prior anti-tumor treatment, and within 28 days of first dose of study treatment on C1D1, then this may be used for Screening purposes; in such situations it is not necessary to repeat tests if the assessments are of sufficient diagnostic quality.

Tumor assessments (CT or MRI scan) of the chest, abdomen, and pelvis will be done once every 8 weeks (every two cycles) from the day of the first dose for the first six cycles (C3D1, C5D1, C7D1), and once every 12 weeks (every three cycles) thereafter (C10D1, C13D1, etc.). The End of Treatment scan will be done if the previous scan was not done within four weeks (28 days) prior to the End of Treatment visit or if the previous scan did not show radiographic disease progression. The same imaging modality (CT or MRI) must be used throughout the study unless the patient develops a contraindication to the modality used for the Screening scan.

A bone scan (BS), or alternatively a whole-body MRI (WBMRI), should be performed at Screening only in patients with new symptoms (e.g., new persistently-elevated ALP) to assess bone metastasis; screening of asymptomatic patients for clinically unapparent bone metastases is not supported by applicable guidelines (Chen 2020, Vogel 2018, Benson 2017) but may be done at the Investigator's discretion if local routine practice. Patients with positive BS/WBMRI at baseline will undergo further radiological assessments of bone lesions performed at protocol-scheduled time points for tumor assessments (see Appendix 1) and as per institutional practice. Lytic/mixed lesions with

soft-tissue component may be included in the evaluation of disease burden if they meet measurability criteria, while blastic lesions are considered non-measurable, in accordance with RECIST 1.1.

For patients with PR or CR, the Investigator should make every attempt to perform the confirmation scan 4 to 5 weeks after the last scan was performed. Radiographic PD must be confirmed by central radiology prior to treatment discontinuation if progression is seen on the first or second post-treatment scan.

Patients who discontinue study drug should have a tumor evaluation visit as soon as possible after the event (e.g., clinical deterioration; ± 28 days window). If a previous scan was obtained within 28 days prior to the date of discontinuation, then a scan at treatment discontinuation is not mandatory but recommended if the clinical situation indicates an altered disease status. For patients who discontinue study treatment due to documented PD, this is the final required tumor imaging.

Patients who discontinue study drug for a reason other than radiographic disease progression, withdrawal of consent, death, or loss to follow-up should continue tumor evaluation visits if possible every 12 weeks until they start another anti-cancer therapy, experience disease progression, withdraw consent, die, or are lost to follow-up.

Standard imaging studies should be performed according to the imaging manual provided by the central imaging laboratory designated by the Sponsor. Tumor response will be evaluated per RECIST version 1.1 (see Appendix 6).

## 6.10 Patient-reported outcomes

HRQOL and symptom response will be measured using the EORTC QLQ-C30 QLQ-BIL21, the EQ-5D, and the G-SET/HTI. Guidelines for completion of these instruments are provided in Appendix 7.

The EORTC QLQ-C30 measures five functional dimensions (physical, role, emotional, cognitive, and social), three symptom scales (fatigue, pain, and nausea and vomiting), six single symptom items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact), and global health and quality-of-life.

It will be administered in conjunction with a disease-specific quality of life questionnaire QLQ-BIL21, which is the only scale focusing specifically on the HRQoL of patients with cholangiocarcinoma. The EORTC QLQ-BIL21 comprises five multi-item measures of cholangiocarcinoma and gallbladder cancer-associated symptoms (eating symptoms, jaundice, tiredness, pain symptoms, anxiety), and three single items on treatment side effects, difficulties with drainage bags/tubes, and concerns regarding weight loss (Kaupp-Roberts 2016).

The EQ-5D is a standardized instrument measuring health outcomes, with five health state dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D also includes a graded vertical visual analog scale (VAS) on which the patients rate their general state of health at the time of the assessment.

The G-SET/HTI is a single item, and will be used as an external anchor to determine the minimal important difference of the EQ-5D VAS, EORTC QLQ-C30, and QLQ-BIL21 scales. It will be administered twice during the study, consistent with the protocol by the EORTC Quality of Life Group (Musoro 2018) for evaluating the minimal important difference. The G-SET/HTI will be provided after 8 weeks (at Cycle 3 Day 1) and 16 weeks (at Cycle 5 Day 1). The G-SET/HTI is a patient-rated change in health between two time periods using a five-point ordinal scale (1=much better now than 8 weeks ago; 2=somewhat better now than 8 weeks ago; 3=about the same as 8 weeks ago; 4=somewhat worse now than 8 weeks ago; 5=much worse now than 8 weeks ago) (adapted from Ware 2002, Lloyd 2014).

The QLQ-C30, QLQ-BIL21, and EQ-5D questionnaires will be provided to the patients to complete before the first dose on Day 1 of the first cycle, every 8 weeks (two cycles) for the first six cycles (C3D1, C5D1, C7D1), once every 12 weeks (three cycles) thereafter (C10D1, C13D1, etc.), at the End of Treatment visit, and at the 30-day Safety Follow-up visit. The G-SET/HTI will be provided after 8 weeks (at Cycle 3 Day 1) and 16 weeks (at Cycle 5 Day 1). The questionnaires should be completed by the patient without assistance during the scheduled visit, before the patient sees the physician (i.e., at the start of the visit), with the EQ-5D to be completed first.

## 6.11 Protocol deviations

The Investigator should conduct the study in compliance with the protocol which was given approval/favorable opinion by the IRB/IEC and where applicable by the regulatory authorities except where necessary to eliminate immediate hazards to the patient.

A deviation to any protocol procedure, or waiver to any stated criteria will not be allowed in this study. The Sponsor must be notified of all intended or unintended deviations to the protocol (e.g., inclusion/exclusion criteria, dosing, missed study visits) on an expedited basis.

The Investigator or designee should document all protocol deviations and explain (if possible) any deviation from the approved protocol.

Any data recorded on the study eCRF will be collected and included in the database according to Clinical Data Interchange Standards Consortium (CDISC) standards and subjected to the same procedures as other data. If a patient was ineligible or received an incorrect dose or investigational treatment and had at least one administration of investigational product, data should be collected for safety purposes.

The Investigator should notify the IRB/IEC of deviations from the protocol in accordance with local procedures.

# 7 TREATMENT

## 7.1 Investigational product

Derazantinib is an investigational oral drug supplied as 100 mg capsules.

The Investigator must ensure that derazantinib capsules will be used only in accordance with the protocol.

### 7.1.1 Labeling and packaging

Derazantinib is supplied as capsules in bottles and labeled in the local languages as investigational agent, according to relevant guidelines. The Sponsor will provide derazantinib capsules required for completion of this study. It will be shipped to the pharmacist/study personnel at the clinical sites during the study through the Interactive Response Technology (IRT) system.

### 7.1.2 Drug accountability

When a drug shipment is received, the Investigator or designee will check the amount and condition of the drug, check for appropriate local language in the label, drug expiration date, and acknowledge receipt in the IRT system. A Packing Slip will be included with the shipment and must be completed upon receipt and returned as instructed on the form. In addition, the Investigator or designee shall contact the Sponsor as soon as possible if there is a problem with the shipment.

A Drug Accountability Log will be provided for derazantinib capsules. The log must be kept current and should contain the protocol number, the name and clinical site of the Investigator, dates and quantities of drug received, patient's identification number to whom derazantinib capsules were dispensed, the date and quantity dispensed, and balance remaining, if from individual patient drug units, as well as the lot number, dose, and the initials of the dispenser. Drug accountability is performed to the capsule level.

To avoid unnecessary waste of derazantinib capsules, in cases where treatment was interrupted and/or dose was reduced, the patient can continue dosing from the previously dispensed bottle until the next drug dispensing visit where re-supply is needed to maintain the protocol dosing regimen.

At the end of the study or as directed, all study drug, including unused, partially used, or empty containers, will be returned to the designee as instructed by the Sponsor. Derazantinib capsules will be returned only after the study monitor has completed a final inventory to verify the quantity to be returned. The return of derazantinib capsules must be documented and the documentation must be included in the shipment. Unused drug supplies may be destroyed by the Investigator when approved in writing by the Sponsor and the Sponsor has received copies of the site's drug handling and disposition Standard Operation Procedures (SOPs) or equivalent.

All derazantinib capsules inventory forms must be made available for inspection by a Sponsor authorized representative or designee and regulatory agency inspectors. The Investigator is responsible for the accountability of all used and unused study supplies at the site.

### 7.1.3 Storage and handling

Drug supplies must be stored in a secure, limited access storage area. Derazantinib capsules are stable when stored at controlled room temperature per storage instructions provided in the label.

If storage conditions deviate from the above storage requirements, the Investigator will document the deviation and inform the study monitor within 24 hours of discovery of the deviation. The supplies should be held and not dispensed until the deviation has been reviewed by the Sponsor's Quality Assurance or designee. If it is determined that the product is no longer suitable for use, the bottles must be reported as damaged in the IRT and a resupply shipment will be made.

### 7.1.4 Derazantinib administration

Derazantinib capsules will be administered once a day, by mouth. All patients will dose at 300 mg once daily (QD) unless a dose reduction is required. Derazantinib capsules must be administered 1 hour before, or at least 2 hours after, a meal, except in the rich PK patient subset, who will be fasted on Day 1 of Cycle 1 (first dose), when derazantinib will be administered after at least 10 h from the last meal, and no food will be taken during the 4 h following derazantinib administration.

In the event of nausea or vomiting which is assessed as at least CTCAE Grade ≥ 2, a light meal before subsequent derazantinib administration is allowed, to minimize the severity of the event.

For administrative reasons, the treatment period is defined by 4-week cycles (28 days).

For an individual patient, treatment will continue until death, disease progression (clinical or radiological), unacceptable toxicity, or another discontinuation criterion is met. It isexpected that most patients will receive derazantinib capsules for 1 to 8 months.

## 7.2 Missed or vomited doses

A missed or vomited dose should not be replaced. The patient should be instructed to take the next scheduled dose at the regularly scheduled time. If the patient vomited the first dose of derazantinib, the patient may be re-challenged at the Investigator's discretion.

Only if a derazantinib dose is vomited within 2 hours of administration, this should be considered as a missed dose and reported in eCRF.

## 7.3 Dose modifications for drug-related toxicities

### 7.3.1 General recommendations

In general, once the dose of derazantinib has been modified for a patient, all subsequent cycles should be administered to that patient at the modified dose. The modified dose will be considered the maximum dose for all subsequent cycles for that patient.

When a drug-related toxicity is observed, dose delays and/or reductions in derazantinib administration are allowed. A drug-related toxicity is defined as any toxicity considered definitely, probably, or possibly related to derazantinib, or when the relationship is

unknown. If dose reduction is indicated, a patient should be assigned to the lower dose. Dose re-escalation is not permitted. In the event of a dose modification, the dose change(s) must be captured in the EDC system. If questions or considerations regarding dose modification arise or a specific dose modification is needed, the Sponsor's Medical Monitor or designee should be consulted.

In the event of nausea or vomiting (both assessed as potential risks for derazantinib), which is assessed as at least CTCAE Grade ≥ 2, a light meal before subsequent derazantinib administration is allowed, to minimize the severity of the event; immediate dose modifications upon CTCAE Grade ≥ 2 nausea or vomiting are not recommended, subject to the Investigator's discretion and medical judgement.

**Table 3 Dose delays/reductions for drug-related toxicity not otherwise specified**

| Event grade | Action |
|---|---|
| Grade 1 or 2 | Continue current dose level, unless dose interruption/modification may be clinically indicated (as assessed by the Investigator and agreed upon by Medical Monitor or designee) |
| Grade 3 | Withhold derazantinib until recovery to Grade 1 or baseline. Administer derazantinib at the next lower dose for subsequent dosing, unless further dose reduction is required |
| Grade 4 | Permanently discontinue derazantinib if the event is at least possibly related to derazantinib. |

**Table 4 Derazantinib dose reduction scheme**

| Current dose | Dose after reduction |
|---|---|
| 3 capsules QD (300 mg daily) | 2 capsules QD (200 mg daily) |
| 2 capsules QD (200 mg daily) | 1 capsule QD (100 mg daily) |
| 1 capsule QD (100 mg daily) | 1 capsule QOD (100 mg every other day) |

### 7.3.2 Hyperphosphatemia

Because hyperphosphatemia is not defined by CTCAE v. 4.03, for the purpose of this protocol hyperphosphatemia is defined as:

Grade 1: > ULN to < 7.0 mg/dL (< 2.26 mmol/L)

Grade 2: Non-invasive intervention required (e.g., withhold drug or modify dose) orbetween 7.0 – 9.0 mg/dL (2.26 – 2.90 mmol/L)

Grade 3: Severe or medically significant, but not immediately life threatening, or > 9.0 – 10.0 mg/dL (> 2.90 – 3.23 mmol/L)

Grade 4: Life-threatening consequences, urgent intervention indicated e.g., dialysis or > 10.0 mg/dL (> 3.23 mmol/L)

Table 5 guides interventions for the management of hyperphosphatemia considered at least possibly related to derazantinib. For all patients, it is recommended to restrict phosphate intake to 600–800 mg daily.

**Table 5 Dose delays/reductions for drug-related hyperphosphatemia**

| **Serum phosphate level** | **Action**<br>*(For serum phosphate ≥ 7.0 mg/dL, consider adding an oral phosphate binding/reducing agent until serum phosphate level returns to < 5.6 mg/dL)* |
|---|---|
| < 7.0 mg/dL (< 2.26 mmol/L) | Continue derazantinib at current dose. |
| 7.0 – 9.0 mg/dL (2.26 – 2.90 mmol/L) | Withhold derazantinib with weekly reassessments until the level returns to < 5.6 mg/dL; the patient may restart derazantinib at the dose prior to hyperphosphatemia. If hyperphosphatemia lasts > 2 weeks, consider restarting at the next lower dose. |
| > 9.0 – 10.0 mg/dL (> 2.90 – 3.23 mmol/L) | Withhold derazantinib with weekly reassessments until the level returns to < 5.6 mg/dL; the patient may restart at the next lower dose level. |
| > 10.0 mg/dL (> 3.23 mmol/L) or significant alteration from baseline renal function; or<br>Grade 3 hypercalcemia | Withhold derazantinib with weekly reassessments until the level returns to < 5.6 mg/dL; the patient may restart at two dose levels lower, or permanently discontinue derazantinib (e.g., if considered life threatening event). |

### 7.3.3 Management of retinal adverse events

A complete ophthalmological examination (see Section 6.3) should be performed by an ophthalmologist at the Screening visit, for the first four cycles (i.e., Day 1 of Cycles 2–5), and at the End of Treatment visit. Further complete ophthalmological examinations only need to be performed if clinically indicated. Table 6 provides specific guidance for the management of dose delays/reductions in the case of retinal adverse events possibly related to derazantinib.

**Table 6 Dose delays/reductions for drug-related opthalmological toxicity (central serious retinopathy / retinal pigment epithelial detachment)**

| **Grade** | **Action** |
|---|---|
| Asymptomatic clinical or diagnostic observations only (Grade 1) | Withhold derazantinib until resolution. If the event resolves within 4 weeks, restart at the next lower dose level. If stable but not resolved for two consecutive opthalmological examinations, restart at the next lower dose level. |
| Visual acuity 20/40 or better or<br>≤ 3 lines of decreased vision from baseline (Grade 2) | Withhold derazantinib until resolution. If the event resolves within 4 weeks, the patient may restart at the next lower dose level. |
| Visual acuity worse than 20/40 or<br>> 3 lines of decreased vision from baseline (Grade 3) | Withhold derazantinib until resolution. If the event resolves within 4 weeks, the patient may restart at two dose levels lower. If the event recurs, consider permanent discontinuation of derazantinib. |
| Visual acuity 20/200 or worse in affected eye (Grade 4) | Permanently discontinue derazantinib. |

### 7.3.4 Management of QTc prolongation or other significant ECG abnormalities

If significant QTc prolongation and/or significant ventricular arrythmia is observed, i.e., a prolonged QTc interval ≥ 501 msec on at least two separate ECGs (consistent with a CTCAE v4.03 Grade 3 event), derazantinib must be withheld, and the patient must be monitored by the investigator and hourly (triplicate) 12-lead ECG obtained until the QTc has returned to ≤ 470 msec. The clinical context and possible factors contributing to QTc prolongations such as electrolyte abnormalities (potassium, calcium or magnesium), concomitant medications, or other clinical factors such as cardiac ischemia must be carefully assessed, and any findings documented in the eCRF. The decision to continue treatment with derazantinib should be reviewed and supported by a cardiologist.

Once QTc prolongation has resolved, and if a decision was made to continue treatment with derazantinib, patients may continue treatment at a lower dose with an ECG monitoring schedule defined by the cardiologist.

Patients who experience a QTc interval ≥ 501 msec on at least two separate ECGs after dose reduction will be discontinued from study.

All significant QTc prolongations or other relevant ECG abnormalities, will also be evaluated centrally.

## 7.4 Treatment compliance

All doses given during the patient's visits with the Investigator will be administered under the supervision of clinical study personnel. The patients will be instructed to return all unused study drug at the next visit. Compliance to the study drug regimen will be evaluated by counting unused capsules.

$$\% \text{ compliance} = \frac{\#\text{ of capsules dispensed} - \#\text{ of capsules returned}}{\#\text{ of capsules prescribed/day}^{a} \times \#\text{ of days}^{b} \text{ in the dosing interval}} \times 100$$

[a] Number of capsules prescribed (i.e., 3 or as determined per the dose reduction guidelines for toxicity considered related to derazantinib and specified in the eCRF

[b] Number of days during that interval that the patient should have dosed (i.e., excluding any days that the patient was instructed to hold dosing due to an AE)

During the treatment period, if compliance is not between 80% and 120%, inclusive, the patient will be counseled about the importance of adherence to the mandated regimen. If the patient continues to be noncompliant in terms of dosing, the patient may have to be discontinued from the study treatment.

Administration of derazantinib capsules will be recorded in the Drug Accountability Log and eCRF. Patients must return empty bottles and remaining capsules. Returned capsules must be recorded in the Drug Accountability Log which is supplied to the site.

At each visit after the study treatment is initiated, the Investigator or designee must record the date, interval between visits, quantity and strengths, and any dose changes/interruptions of study drug dispensed/administered. To avoid unnecessary waste of derazantinib capsules, in cases where treatment was interrupted and/or dose was reduced, the patient can continue dosing from the previously dispensed bottle until the next drug dispensing visit where re-supply is needed to maintain the protocol dosing regimen.

## 7.5 Blinding

This is an open-label study. Neither the patient, the Investigator/site staff, nor the Sponsor will be blinded to the treatment administered.

## 7.6 Prior treatment

Reasonable efforts will be made to determine all relevant prior treatments received by the patient within 30 days prior to the first derazantinib dose, including accurate start and stop dates of the regimens. All relevant information must be recorded in the appropriate patient's eCRF. All surgical procedure history, prior chemotherapy, and radiation therapy must be recorded on the appropriate eCRF.

## 7.7 Concomitant treatments

All information regarding concomitant treatments (medications or procedures) must be recorded on the patient's eCRF (including the name of the medication or procedure and duration of treatment). Complete information of analgesics and acid-reducing agents' consumption should be obtained and recorded.

### 7.7.1 Permitted treatment

Palliative and supportive care for disease-related symptoms will be offered to all patients. In addition, the following treatments are allowed:

- Standard therapies for concurrent medical conditions
- Erythropoietin Stimulating Agents (ESA): Please follow the American Society of Clinical Oncology (ASCO), the American Society of Hematology, MEDICARE guidelines for the use of epoetin in patients with cancer and Food and Drug Administration (FDA) alerts dated 09 March 2007, 08 November 2007, 12 March 2008, 31 July 2008, and 02 December 2008.
- Hematopoietic growth factors, including filgrastim (Neupogen®), or other granulocyte colony stimulating factors (G-CSF). Please follow ASCO guidelines for the use of white blood cell growth factors (http://jco.ascopubs.org/content/24/19/3187.full).
- Prophylactic antiemetics may be administered according to standard practice
- Megestrol acetate (Megace®)
- Use of topical corticosteroids, topical and systemic antibiotics according to standard of care (SOC) or institutional guidelines
- Treatment with non-conventional therapies (i.e., herbs or acupuncture) and vitamin/mineral supplements are acceptable, provided that they do not interfere with the study endpoints, in the opinion of the Investigator
- Bisphosphonates and denosumab for bone metastases or hypercalcemia of malignancy
- Palliative radiotherapy for non-hepatic local pain control provided that, in the opinion of the Investigator, the patient does not meet the criteria for treatment discontinuation (i.e., clear progression of disease)

### 7.7.2 Prohibited treatment / treatment to be avoided or used with caution

The following treatments are not allowed during the study:

- Any concurrent anti-cancer therapy including chemotherapy, radiotherapy, hormonal, targeted therapy, or immunotherapy
  - Palliative radiotherapy for non-hepatic local pain-control may be allowed, provided the patient does not meet criteria of progressive disease and treated lesions will not be included in the target/non-target lesion assessment
- Other investigational agents
- Immunosuppressive therapies, including systemic corticosteroids (except up to a 25 mg/day prednisone-equivalent dose or when used intermittently in an antiemetic regimen, for CNS metastases management or as premedication for imaging studies)

The following treatments should be avoided, if possible, or used with caution during the study:

- Derazantinib may inhibit CYP2C8, CYP1A2, or CYP2D6 metabolism, hence co-administration of derazantinib with drugs known to be substrates of CYP2C8, CYP1A2, or CYP2D6 should be avoided or used with caution (see Appendix 4)
- Derazantinib may be a substrate and inhibitor of human P-glycoprotein (P-gp), therefore co-administration of derazantinib with drugs known to be P-gp substrates with narrow therapeutic index should be avoided or used with caution (see Appendix 5)
- Drugs with known liver toxicity, e.g., clotrimazole, should be avoided or used with caution; if such drugs need to be administered, LFT should be done every 4–5 days during the drugs' co-administration
- Drugs with the potential to prolong QT interval (see Appendix 9)

## 7.8 Potential risks and benefits for study participants

Derazantinib, a multi-kinase inhibitor with activity against FGFR1, FGFR2, mutant FGFR2, FGFR3, and mutant FGFR3 kinases, has demonstrated efficacy and an acceptable safety profile in nonclinical studies. In clinical trials in iCCA (Mazzaferro 2018, Papadopoulos 2017, Droz dit Busset 2020), derazantinib has been shown to be active with a manageable safety profile. It is therefore expected that patients may derive a benefit from derazantinib monotherapy in the current study.

Hyperphosphatemia, fatigue, ocular disorders, gastrointestinal disorders (constipation, diarrhea, nausea, vomiting, stomatitis, and dry mouth), transaminase elevation, hypertension, creatinine increased / renal disorders, hyponatremia, nail toxicities and alopecia are the most frequently reported adverse drug reactions (ADRs) with FGFR inhibitor treatments (Chae 2017, Katoh 2019, Balversa® USPI, Pemazyre® USPI), and are considered to be FGFR inhibitor class effects. Of these, hyperphosphatemia, fatigue, ocular disorders, blood creatinine increased/renal disorders, hyponatremia, and nail toxicities are assessed as important potential risks for derazantinib, and increased transaminases is assessed as an important identified risk for derazantinib. The following events are assessed as potential risks for derazantinib: QT prolongation, gastrointestinal disorders, hypertension, and alopecia. Gastrointestinal disorders, and hypertension can be monitored

and are mostly manageable, and the event alopecia has no significant impact on the condition of the patients. Non-clinical and clinical data on QT prolongation rule out a large (i.e., mean effect > 20 ms) effect of derazantinib on QTcF. There have been no serious events / arrhythmias reported as being consequent to QT prolongation, and the risk is mostly preventable with the implemented routine risk minimization measures. As the safety data are accumulating and remain subject to final evaluation for ongoing studies with derazantinib, the Sponsor will continue to evaluate safety data to characterize further potential risks and assess identified risks.

# 8 SAFETY ASSESSMENTS

## 8.1 Definitions

### 8.1.1 Adverse events

An AE is defined as any untoward medical occurrence in a patient or clinical investigational subject administered a pharmaceutical product, and that does not necessarily have a causal relationship with study-drug treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

### 8.1.2 Serious adverse events

An SAE is any adverse experience occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening
- Requires new inpatient hospitalization defined as a hospital admission lasting > 24 hours (not including emergency room visit without hospital admission), or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above. An important medical event may be considered an SAE based upon appropriate medical judgment.

### 8.1.3 Unexpected adverse event or serious adverse event

An unexpected AE or SAE is one for which the nature or severity of the event is not consistent with the applicable product information, as summarized in the Investigator's Brochure.

### 8.1.4 Suspected unexpected serious adverse reactions

All AEs that are determined by the Investigator or by the Sponsor as having a reasonable suspected causal relationship to a study drug and that are both unexpected and serious are considered to be suspected unexpected serious adverse reactions (SUSARs), and are subject to expedited regulatory reporting.

### 8.1.5 Inpatient hospitalization

An inpatient hospitalization is a hospital admission that lasts more than 24 hours.

### 8.1.6 Study drug-related adverse event or serious adverse event

A study drug-related AE or SAE is defined as an AE or SAE that is definitely, probably, or possibly related to the treatment with derazantinib, or when the relationship is unknown.

### 8.1.7 Further adverse event and serious adverse event definitions

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE.

Laboratory data are to be collected as stipulated in Section 6.5. Clinical syndromes associated with laboratory abnormalities are to be recorded as appropriate (e.g., diabetes mellitus instead of hyperglycemia).

Scheduled hospitalizations or elective surgical for a pre-existing condition that is unrelated to the disease under study and has not worsened are not considered SAEs.

Prolongation of a scheduled hospitalization is considered an SAE.

Complications associated with scheduled procedures are considered AEs or SAEs.

Progression of disease is considered an efficacy outcome parameter and should not be captured as an AE or SAE unless its outcome is death.

Adverse events, that occur following the execution of the ICF but prior to dosing must be recorded in the medical history page of the eCRF; if serious, these must be reported as SAEs as described in Section 8.4. Adverse events, including SAEs, that occur after patients receive any anti-cancer therapy in the follow-up period, other than the study-defined treatments, will not be recorded as AEs or SAEs.

## 8.2 Responsibilities and procedures

The responsibility for the safety of an individual patient lies in all cases with the Investigator. This includes the timely review of all safety data obtained during the course of the study.

An Investigator must instruct his/her patients to report any AE and SAE they experience.

Investigators capture, evaluate, and document all AEs and SAEs occurring during a patient's enrollment in the study, commencing with the first day of treatment and including the protocol-defined 30-day post-treatment follow-up period, as source documents and on designated eCRF pages. SAEs related to study-specific procedures (e.g., tissue biopsy) will be reported from the date of signing the informed consent.

Investigators should assess AEs at each scheduled and non-scheduled visit, by the use of open-ended questioning, physical examination, and review of laboratory results.

Note: It is important to record all AEs and SAEs that result in temporary and permanent discontinuation of study drug, regardless of severity.

Investigators must report all SAEs, whether or not they are considered study-drug related, to the Sponsor or designee within 24 hours from knowledge of the event (see Section 8.4).

In cases of SUSARs, Investigators are responsible for reporting to their local IRB/IEC; the Sponsor or designee(s) is responsible for notifying regulatory authorities and all relevant Investigators.

## 8.3 Adverse event and serious adverse event assessment criteria

Adverse events and SAEs are evaluated and graded using NCI CTCAE guidelines, version 4.03. See also Section 8.6.

## 8.4 Serious adverse event reporting

The Investigators are obligated to immediately report to [redacted] the drug safety designee of the Sponsor, each SAE that occurs during this investigation, within 24 hours from knowledge of the event, whether or not it is considered study-drug related. All requested supplementary documents (e.g., discharge letter, autopsy report, etc.) and/or relevant data (e.g., ECG, laboratory tests, discharge summaries, post mortem results, etc.) must be faxed or e-mailed within 24 hours from the time documents become available. If any questions or considerations regarding an SAE arise, the Sponsor's Medical Monitor or designee should be consulted.

| Safety Vendor | Sponsor's Medical Monitor |
|---|---|
| [redacted] | [redacted] |

The information provided in an SAE report should be as complete as possible, but contain a minimum of:

- A short description of the AE (diagnosis) and the reason why the AE was categorized as serious
- Patient identification and treatment (if applicable)
- Investigator's name and phone number (if applicable)
- Name of the suspect medicinal product and dates of administration
- Assessment of causality

If all information about the SAE is not yet known, the Investigator will be required to report any additional information within 24 hours as it becomes available.

All SAEs will be evaluated by the Sponsor's Medical Monitor or designee. In the case of a SUSAR, the Sponsor or designee will report the event to all pertinent regulatory authorities having jurisdiction over ongoing derazantinib trials in an expedited manner (within 7 days or 15 days of knowledge) and to all Investigators involved in derazantinib clinical trials.

The Investigators must in turn notify their governing IRB/IEC.

## 8.5 Post-treatment safety follow-up

In this study, the post-treatment safety follow-up period is defined as at least 30 days after the last dose of assigned treatment.

All patients will be followed for a minimum of 30 days after discontinuation of the study drug. However, if a patient receives other anticancer therapy within the 30-day follow-up period, the follow-up for AEs will cease, beginning on the first day of the new therapy. Note: Survival follow-up will continue.

Unresolved study-drug-related AEs and SAEs at the end of the 30-day safety follow-up period will be followed until they have, in the opinion of the Investigator, resolved to baseline or CTCAE Grade 1, stabilized, or are deemed to be irreversible.

After the follow-up period, only study-drug-related SAEs must be collected and reported; these must also be followed until they have, in the opinion of the Investigator, resolved to baseline or CTCAE Grade 1, stabilized, or are deemed to be irreversible.

## 8.6 Grading of severity

Each AE or SAE will be graded for severity according to NCI CTCAE (version 4.03). The criteria can be found at http://ctep.cancer.gov/reporting/ctc.html.

For AEs not listed in the NCI CTCAE version 4.03, a similar grading system should be used as follows:

- Grade 1: Mild AE
- Grade 2: Moderate AE
- Grade 3: Severe AE
- Grade 4: Life-threatening or disabling AE
- Grade 5: Death

For AEs that can be described by the NCI CTCAE guidelines, the NCI CTCAE Grade 4 (life-threatening or disabling AE) is assessed based on unique clinical descriptions of severity for each AE, and these criteria may be different from those used for the assessment of AE seriousness. An AE assessed as Grade 4 based on the NCI CTCAE grades may or may not be assessed as serious based on the seriousness criteria.

## 8.7 Assessment of causality

The relationship between an AE and derazantinib will be determined by the Investigator on the basis of his/her clinical judgment and following definitions:

### 8.7.1 Related adverse events

- The AE follows a reasonable temporal sequence from study drug administration and cannot be reasonably explained by the patient's clinical state or other factors (e.g., disease under study, concomitant diseases, concomitant medications)
- The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its chemical group, or is predicted by known pharmacology, a known reaction to agent, or chemical group
- A related AE is any AE considered related to derazantinib, i.e., definitely, possibly, or probably related to derazantinib.

### 8.7.2 Not related adverse events

- The AE does not follow a reasonable temporal sequence from study product administration, or can be reasonably explained by the patient's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).

## 8.8 Contraception and pregnancy

Derazantinib may have adverse effects on a fetus *in utero*, and may have transient adverse effects on the composition of sperm.

### 8.8.1 Contraception

Participants in this study must be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study. In order to be enrolled in the study, both male and female patients of child-producing potential must agree to the contraception requirements in Inclusion criterion 9, and must comply with these requirements from the day of first study medication, or for oral contraception from 14 days prior to the first study medication, throughout the study period, and until at least 120 days after administration of the last dose of study medication.

If there is any doubt that a patient of child-producing potential will reliably comply with the requirements for contraception, the patient should not be enrolled in the study.

### 8.8.2 Pregnancy testing

Serum pregnancy testing will be performed for women of child-producing potential at the Screening visit (within 72 hours prior to dosing), and the End of Treatment visit (see also Section 6.5). In addition, serum- or urine pregnancy testing will be performed monthly (on Day 1 of each treatment cycle) while the patient receives study treatment, at the 30-day Safety Follow-up visit, and until 120 days after the last administration of study drug. Pregnancy testing after the End of Treatment may be performed at the patient's local gynecologist to reduce the burden related to study visits at the site, but must be communicated to the study investigator.

### 8.8.3 Pregnancy

If a female patient inadvertently becomes pregnant while on study drug treatment, the patient must be immediately discontinued from the study.

The Investigator must contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy must be reported to the Sponsor without delay, and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The Investigator must make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If possible, the newborn should be followed up for 8 weeks after delivery.

If a male patient impregnates his female partner, the Investigator must be informed immediately, and the pregnancy reported to the Sponsor and followed up as described above.

### 8.8.4 Nursing women

As it is unknown whether derazantinib is excreted in human milk, because of the potential for serious adverse reactions in the nursing infant, patients who are breast-feeding are not eligible for enrollment in this study under Exclusion criterion 14.

## 9 QUALITY CONTROL AND ASSURANCE

The study will be conducted under the Sponsorship of Basilea. Derazantinib capsules, clinical supplies, and eCRFs will be supplied by the Sponsor or its representative. Representatives of the Sponsor will monitor the study to verify study data, medical records, and eCRFs in accordance with current ICH GCP and other applicable regulations and guidelines.

## 10 PLANNED STATISTICAL METHODS

Details of the statistical analyses presented below will be provided in the study's statistical analysis plan (SAP). A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters a principal feature of the protocol. The SAP will be finalized prior to database lock. Any changes to the methods described in the plan will be described and justified in the final clinical study report.

### 10.1 Study populations

Four analysis populations will be defined as follows:

- Safety/ITT Population: All patients who receive any amount of study drug.
- Modified intent-to-treat (mITT) Population: All patients who receive any amount of study drug and have at least one post-baseline disease assessment.

- Per Protocol Population: All patients in the mITT Population who have no major protocol violations during the study, receive at least one cycle (28 doses) of ARQ 087, have at least one post-baseline efficacy measurement, and test positive for *FGFR2* fusion by the central laboratory.
- PK population: All patients who receive at least 1 dose of study drug and have at least one PK sample.
  - Rich PK population (with PK parameter determination): All patients enrolled in the subset who receive at least 1 dose of study drug and have at least one PK sample.
  - Urine excretion population: All patients who provide a full 24 h interval urine collection on Day 1 of Cycle 2.

## 10.2 Demographics, medical history, baseline characteristics, and concomitant medications

Demographics, baseline characteristics, and medical history information will be summarized for the Safety population using descriptive statistics. No formal statistical comparisons will be performed.

Demographic, baseline characteristics, and medical history data for each patient will be provided in data listings.

## 10.3 Safety analyses

The following key safety parameters will be evaluated:

- Incidence of TEAEs
- Changes in clinical laboratory parameters, CTCAE graded laboratory toxicities, vital signs, ECOG performance status, ECG parameters, physical examinations, and usage of concomitant medications

All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) coding system and displayed in tables and data listings using system organ class (SOC) and preferred term (PT). Analyses of AEs will be performed for those events that are considered treatment-emergent, where treatment-emergent is defined per protocol as any AE or SAE with onset beginning on the day of administration of the first dose of study drug, throughout the treatment period until 30 days after cessation of study treatment (or until the start of alternate anticancer therapy, whichever occurs earlier), or any event that was present at baseline but worsened in intensity or was subsequently considered drug-related by the Investigator through the end of the study.

The number and percentage of patients with any TEAE, with any TEAE assessed by the Investigator as related to treatment (definite, probable, or possible relationship to derazantinib, or the relationship is unknown), and with any SAE will be summarized for all enrolled patients. In these tabulations, each patient will contribute only once to each of the incidence rates in the descriptive analysis, regardless of the number of episodes. No formal hypothesis-testing analysis of AE incidence rates will be performed.

All AEs occurring on-study will be listed in patient data listings. By-patient listings also will be provided for the following: patient deaths, SAEs, and AEs leading to withdrawal.

Abnormal findings from physical exams and lab tests will be analyzed using descriptive analyses.

## 10.4 Pharmacokinetic analyses

All patients enrolled in the rich PK subset who receive at least 1 dose of study drug and have at least one PK sample will be included for the determination of PK parameters by non-compartmental analysis. The following parameters will be determined: $C_{max}$, $t_{max}$, $AUC_{0-24}$, $AUC_{last}$. Of these patients, those that provide 24 h interval urine samples on Cycle 2 will be included for the determination of urinary excretion parameters: Ae, Ae%, CLR.

Plasma concentrations and PK parameters will be summarized with descriptive statistics, including mean, standard deviation, coefficient of variation, median, geometric mean, coefficient of variation of geometric mean, minimum and maximum.

In all other patients who receive at least one dose of study drug and have at least one PK sample, plasma concentrations will be summarized separately with descriptive statistics , including mean, standard deviation, coefficient of variation, median, geometric mean, coefficient of variation of geometric mean, minimum and maximum.

A PopPK analysis will be performed with the possibility of pooling PK data from other clinical studies. A separate PopPK analysis report will be provided.

## 10.5 Pharmacodynamic analyses

Summary statistics including mean, standard deviation, median, coefficient of variation, minimum and maximum for baseline, each post-baseline measurement, and change from baseline will be performed on serum tumor markers and biomarkers (e.g., CA19.9, CEA, CA125, FGF19, FGF21, FGF23) utilizing standard blood chemistry methodologies and enzyme-linked immunosorbent assay (ELISA)-based assays.

To explore the association of blood concentration with clinical outcome, the above descriptive statistics of tumor markers and biomarkers will also be presented separately for each response category (CR, PR, and stable disease [SD] combined vs. PD). Logistic regression will also be utilized if appropriate.

## 10.6 Efficacy analyses

All efficacy endpoints will be summarized on the data from patients. All analyses will include summary statistics, including number of patients (n) and percentage (%) for categorical variables and number of patients, mean, standard deviation, median, minimum, and maximum for continuous variables. Two-sided exact 95% confidence intervals (CIs) based on the large sample assumption will be provided where appropriate. Time-to-event analyses will be performed using Kaplan-Meier (KM) methods.

### 10.6.1 Primary efficacy parameter

**Substudy 1**

The primary efficacy endpoint will be ORR, defined as the achievement of confirmed CR or PR using RECIST v1.1, as assessed by the central radiology reviewers. Point estimates and 2-sided 95% CIs will be provided. Hypothesis testing will be performed for H0: ORR=0.1 versus Ha: ORR=0.23 at the interim and final analyses as specified:

The decision rules are specified as:

- If the interim one-sided p-value, p1 > 0.5 (i.e., the observed ORR is less than 10%), the trial will stop due to futility; otherwise, the trial will continue to the second stage. At the final stage, if the p-value is ≤ to 2.5% (one-sided), or equivalently the lower limit of the CI is ≥ 10%, the null hypothesis will be rejected.

In the final analysis, the ITT population will be the primary analysis population.

**Substudy 2**

The primary efficacy endpoint will be progression-free survival at 3 months (PFS 3) based on survival status or central radiology review RECIST 1.1. For Substudy 2, a Simon's two-stage design will be used, with approximately 15 patients in Stage 1, and an additional 28 patients if the study proceeds to Stage 2. H0 will be rejected if a PFS 3 is observed in 25 or more of these 43 patients. The type I error rate is 0.0481, and power is approximately 0.8 when the true PFS 3 rate for derazantinib is p1 = 0.65.

The mITT population will be the primary analysis population.

### 10.6.2 Secondary efficacy parameters

Duration of response, PFS and OS will be presented through use of summary statistics using KM methods, to include 25$^{th}$, 50$^{th}$ (median), and 75$^{th}$ percentiles and associated 2-sided 95% CIs for the median, number of events and number of censored observations. PFS will be defined by RECIST v1.1, based on the date of PD that will be used to determine duration. ORR is defined as the achievement of confirmed CR or PR using RECIST v1.1, as assessed by the central radiology reviewers.

Changes in HRQOL and symptom response will be analyzed based on the EORTC QLQ-C30, QLQ-BIL21, and the EQ-5D VAS, primarily using descriptive statistics.

### 10.6.3 Exploratory efficacy analyses

Tumor markers (CA19.9, CA125, CEA) and biomarkers (FGF19, FGF21, FGF23) will be analyzed using descriptive statistics by cycle or visit.

Other analyses such as correlation between tumor and biomarkers, toxicity, responses, outcomes with derazantinib versus prior chemotherapies, and PK parameters will be conducted and will be further described in the Statistical Analysis Plan.

## 10.7 Determination of sample size, interim analysis, and adaptations

**Substudy 1**

To prove the drug effect over placebo in ORR in this single-arm pivotal study, the hypothesis is specified as:

H0: ORR<= 0.10 and Ha: ORR>0.1.

The hypothesis test will be performed at a one-sided 2.5% significance level. A 10% response rate is chosen for the null hypothesis, which is much higher than the observed placebo rate of 7~8% in larger historical trials and publications (Lamarca 2014). A 23% response rate under the alternative hypothesis is estimated for power and sample size calculations.

Approximately 100 patients will be enrolled for this two-stage group sequential study with futility stopping. An interim analysis for futility will be done when 40 patients who satisfy mITT criteria have at least one post-baseline tumor evaluation. The study will be terminated for futility if 4 or fewer responses are observed among 40 evaluable patients. If the treatment is ineffective, i.e., ORR=0.1, the probability of futility stopping is 63%. If the true response rate ORR=0.23, the probability of futility stopping is only 3%. The design will provide approximately 90% power to reject the null hypothesis at one-sided significance level 0.025, or equivalently to have the lower bound of confidence interval of ORR > 10%.

If 5 or more objective responses are observed and confirmed based on central radiology review prior to enrollment of 40 evaluable patients, the interim analysis may be performed based on fewer than 40 patients.

**Substudy 2**

A Simon's two-stage design will be used in Substudy 2. The null hypothesis ($H_0$) that the true 3-month rate of PFS 3 is $p_0 \leq 0.45$ will be tested against a one-sided alternative. In the first stage, approximately 15 mITT-evaluable patients will be accrued. If there are 7 or fewer patients with PFS 3 in these 15 patients, then Substudy 2 will be stopped. Otherwise, 28 additional mITT-evaluable patients will be accrued for a total of up to approximately 43. $H_0$ will be rejected if a PFS 3 is observed in 25 or more of these 43 patients. The type I error rate is 0.0481, and power is approximately 0.8 when the true PFS3 rate for derazantinib is $p_1 = 0.65$.

If the required number of patients alive and without disease progression is reached before full enrollment to Stage 1, the decision to transition from Stage 1 to Stage 2 may be taken before Stage 1 is fully enrolled.

If the required number of patients alive and without disease progression is not reached at the time of full enrollment to Stage 1, further enrollment will be suspended to allow for all patients to be evaluated for PFS 3.

## 10.8 Data Monitoring Committee

The Data Monitoring Committee (DMC) will be established to ensure the safety of study patients and the validity of study results. The DMC composition and operation will be described in the DMC charter. The DMC may recommend study termination or continuation based on periodic review of safety and/or efficacy data in this study.

# 11 COMPLIANCE WITH GOOD CLINICAL PRACTICE AND ETHICAL CONSIDERATIONS

## 11.1 Institutional Review Board or Independent Ethics Committee approval

The protocol, any protocol modifications, the ICF, and, if applicable, permission to use private health information must be approved by the Investigator's IRB/IEC in compliance with Federal regulations 21 CFR §56 prior to study initiation. Documentation of this approval must be provided to the Sponsor or its designee, and made available during an inspection by the FDA or other regulatory agency inspectors. The Investigator will also provide the Sponsor with the General Assurance Number documenting that the IRB/IEC is duly constituted, as well as a list of the names, occupations, and affiliations of the members of the IRB/IEC when available.

Before initiating a trial, the Investigator/institution should have written and dated approval/favorable opinion from the IRB/IEC and, where applicable, competent authorities/regulatory bodies for the trial protocol/amendment(s), written ICF patient recruitment procedures (e.g., advertisements) and written information to be provided to patients.

## 11.2 Compliance with Good Clinical Practice and ethical considerations

This study must be conducted in compliance with IRB/IEC informed consent regulation and the ICH GCP Guidelines. In addition, all local regulatory requirements will be adhered to, in particular those affording greater protection to the safety of the trial participants.

This study will also be conducted according to the current revision of the Declaration of Helsinki, with all subsequent revisions and with local laws and regulations relevant to the use of new therapeutic agents in the country of conduct.

Changes to the protocol will require written IRB/IEC and, where applicable, competent authorities/regulatory bodies approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients.

## 11.3 Patient information and consent

The Investigator (or designee) is responsible for the content of the ICF, but the original and any updated versions must be approved by the Sponsor prior to submission to the IRB/IEC. The ICF should also include any additional information required by local laws relating to institutional review.

Before any study-related procedures are undertaken, the Investigator or designee must obtain written, informed consent from each study participant in accordance with US Federal Regulations (21 CFR §50) and the ICH document 'Guidance for Industry – E6 Good Clinical Practice: Consolidated Guidance.' Informed consent will be obtained by discussing with the patient the purpose of the study, the risks and benefits, the study procedures, and any other information relevant to the patient.

The Investigator or designee must explain to the patient that for purposes of evaluating the study results, that patient's private health information obtained during the study may be

shared with the study Sponsor, regulatory agencies, and IRBs/IECs, before enrolling that patient into the study. It is the Investigator's (or designee's) responsibility to obtain permission to use private health information per the Health Information Portability and Accountability Act (HIPAA) from each patient, or, if appropriate, the patient's legal representative.

The patient or his/her legal representative will document his/her informed consent by signing the current version of the written, IRB-approved ICF in the presence of a witness. The person who conducted the informed consent discussion with the patient and/or patient's legal representative must also sign the ICF. The patient is given a fully executed copy of the ICF bearing all appropriate signatures, and the original must be maintained in the clinical master files at the site.

All active patients participating in the protocol must be re-consented each time the ICF is updated and re-approved by the IRB/IEC.

# 12 STUDY MANAGEMENT AND MATERIALS

The study will be initiated and conducted under the Sponsorship of Basilea. Derazantinib capsules, clinical supplies, and eCRFs will be supplied by the Sponsor or its representative. Representatives of the Sponsor will monitor the study to verify study data, medical records, and eCRFs in accordance with current ICH GCP and other applicable regulations and guidelines.

## 12.1 Monitoring, verification of data, audit, and inspection

A Sponsor monitor or designee will periodically visit each clinical study site to discuss the progress of the clinical trial and to review eCRFs and original source documents for accuracy of data recording, study drug accountability, and correspondence. The extent and frequency of monitoring visits will be determined by the Sponsor or designee based on the status of the trial and the performance of the site. When requested, the Investigator must be available to the study monitor for personal, one-to-one consultation.

Periodically, some or all of the facilities used in the trial may be reviewed or inspected by the IRB/IEC and/or regulatory authorities. An audit or inspection may include, for example, a review of all source documents, drug records, and original clinical medical notes.

The Investigator is to ensure that the trial participants are aware of and consent to the review of personal information during the data verification process, as part of the monitoring/auditing process conducted by properly authorized agents of the Sponsor, or be subject to inspection by regulatory authorities. In addition, participation and personal information is treated as strictly confidential to the extent of applicable law and is not publicly available.

## 12.2 Data recording and retention of study data

In compliance with GCP, the medical records/medical notes, and other study-related materials should be clearly marked and permit easy identification of participation by an individual in a specified clinical trial.

The Investigator is to record all data with respect to protocol procedures, drug administration, laboratory data, safety data, and efficacy ratings on the eCRFs.

If the Investigator relocates or retires, or otherwise withdraws his/her responsibility for maintenance and retention of the master clinical study records, the Sponsor must be notified in writing so that adequate provision can be made with regard to the trial documents.

Trial documents should be retained for at least two years after the approval of a marketing application in an ICH region and until there are no pending or planned marketing applications in an ICH region, or at least two years have elapsed since the formal discontinuation of clinical development of derazantinib by the Sponsor. The documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor that it will inform the Investigator, in writing, as to when the retention of these documents is no longer necessary.

## 12.3 Electronic case report forms

An EDC system will be used to collect the data in this study. The EDC system provides functionality for the clinical sites to enter the data directly into the eCRFs and respond to data discrepancies. Once the data are entered, the information is encrypted and transmitted over the Internet to a clinical trial server where it is electronically reviewed. Any resulting data queries are immediately sent back to the site for resolution. The system automatically keeps a full audit trail of all data changes that occur. The clinical team will undertake additional manual review of the data, but all resulting data queries or clarifications will be entered into the EDC system for resolution. All eCRFs will be completed according to instructions provided in the eCRF Completion Guidelines and ICH GCP guidelines.

## 12.4 Confidentiality, publication, and disclosure policy

The Investigator understands that the Sponsor will use the information developed in the clinical study in connection with the development of derazantinib. This information may be disclosed to other clinical Investigators, the FDA, and other government agencies.

All information disclosed to the Investigator by the Sponsor for the purpose of having the Investigator conduct the clinical trial described in this protocol, or information generated by the Investigator as results in the clinical trial shall be treated by the Investigator as strictly confidential. The Investigator shall not use such information other than for the purpose of conducting the clinical trial and may not disclose such information to others, except when such disclosure is made to colleagues and/or employees who reasonably require the information in order to assist in carrying out the clinical trial and who are bound by like-obligations of confidentiality. Notwithstanding, the Investigator may use or disclose to others any information which: (i) was known to the Investigator prior to the date of its disclosure; (ii) is now, or becomes in the future, publicly available; or (iii) is lawfully disclosed to the Investigator on a non-confidential basis by a third party who is not obligated to the Sponsor or any other party to retain such information in confidence.

The Sponsor acknowledges that the Investigator has certain professional responsibilities to report to the scientific community on findings made in the clinical investigations they conduct. The Investigator shall have the right to publish the results of research performed

under this protocol, provided that such publication does not disclose any Confidential Information or trade secrets of the Sponsor (other than the Data). If the study is conducted as part of a multi-center protocol, the Investigator agrees not to independently publish the findings except as part of an overall multi-center publication, unless specifically approved in writing by the Sponsor or unless more than 12 months have elapsed since the last patient in the study has completed his/her study designed treatment.

# 13 STUDY ADMINISTRATIVE INFORMATION

## 13.1 Sponsor

Basilea Pharmaceutica International Ltd.
Grenzacherstrasse 487
CH-4058 Basel/Switzerland
+ 41 61 606 1111

## 13.2 Global Medical Monitor

[redacted]

## 13.3 Drug Safety

[redacted]

# 14 DOCUMENT HISTORY

| | |
|---|---|
| Original Protocol | 08 December 2016 |
| Amendment 1 | 05 April 2017 |
| Amendment 2 | 13 April 2017 |
| Amendment 3 | 10 October 2017 |
| Amendment 4 | 25 September 2018 |
| Amendment 5 | 19 February 2019 |
| Amendment 6 | 22 July 2019 |
| Amendment 7 | 06 September 2019 |
| Amendment 8 | 17 November 2020 |

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## Appendix 1 Schedule of Assessments

| Tests & Procedures / Visit Name | Pre-Screening Visit | Screening Visit | Cycle 1 | | Cycle 2+ | End of Treatment Visit | 30-day Safety Follow-up | Overall Survival Follow-up |
|---|---|---|---|---|---|---|---|---|
| Day | NA | 0 | 1 | 15 | 1 | Within 7 days after last dose of derazantinib or decision to permanently stop dosing | 30+ days after the last dose of derazantinib | At least every 3 months from date of last dose of derazantinib |
| Window | NA | -28 to -1 | 0 | ± 3 days | ± 3 days | NA | NA | ±14 days |
| Written informed consent | X[1] | X[1] | | | | | | |
| Medical history | X | X | | | | | | |
| QLQ-C30, QLQ-BIL21, EQ-5D, G-SET/HTI questionnaires (prior to seeing physician) | | | X[2] | | X[2] | X[2] | X[2] | |
| Physical examination | | X | X | X | X | X | X | |
| Complete opthalmological examination | | X | | | X[3] | X | X[3] | |
| ECOG performance status | X | X | X | X | X | X | X | |
| Vital signs[4] | | X | X | X | X | X | X | |
| 12-Lead ECG, in triplicate | | X[5] | X[5] | X[5] | X[5] | X[5] | | |
| Blood for clinical blood tests[6] | | X | X | X | X | X | X | |
| Blood for serum pregnancy test | | X[7] | X[7] | | X[7] | X[7] | X[7] | |
| Blood for tumor markers, biomarkers, and ctDNA | | | X[8] | | X[8] | X[8] | | |
| Blood for pharmacokinetics | | | X[9] | X[9] | X[9] | | | |
| Urine for Pharmacokinetics | | | | | X[10] | | | |
| Tumor's genomic status[11] | X | | | | | | | |
| Tumor measurement and staging | | X[12] | | | X[13] | X[14] | | |
| Concomitant medications | | X[15] | X[15] | X | X | X | X | |
| Adverse events assessment | | | X | X | X | X | X | |
| Derazantinib capsule dispensing[16] | | | X | | X | | | |
| Derazantinib capsule accountability | | | | | X | X | | |
| Survival contact[17] | | | | | | | | X |

For footnotes see next page.

[1] Consent can be obtained greater than 28 days prior to first dose and does not have to be repeated unless an updated, approved consent form is available. A patient can consent for tissue analysis and the full study separately or at the same time.

[2] EQ-5D, EORTC QLQ-C30 and QLQ-BIL21 questionnaires should be administered on Day 1 of the first cycle, every 8 weeks (two cycles) for the first six cycles (C3D1, C5D1, C7D1), once every 12 weeks (three cycles) thereafter (C10D1, C13D1, etc.), at the End of Treatment visit and at the 30 day Safety Follow-up. G-SET/HTI questionnaire should be administered on Day 1 of Cycle 3 and Day 1 of Cycle 5. EQ-5D should be completed first, followed by EORTC QLQ-C30, QLQ-BIL21 and G-SET/HTI, when applicable.

[3] Complete opthalmological examination will be performed at C2D1, C3D1, C4D1, C5D1, at the End of Treatment visit, and at the 30-day Safety Follow-up visit, and if clinically indicated (see Section 6.3).

[4] Vital signs include weight, temperature, blood pressure, respiration rate, and pulse. At the Screening visit, height will also be measured (see Section 6.2).

[5] 12-lead ECG in triplicate is required at Screening., on Day 1 and Day 15 of Cycle 1 (pre-dose, and approximately 6–8 hours after the dosing), on Day 1 of Cycle 2 (pre-dose), on Day 1 of Cycle 3 (pre-dose, and approximately 6–8 hours after the dosing), on Day 1 of Cycle 4 and all subsequent cycles (pre-dose), and at the End of Treatment visit (see Section 6.4).

[6] Clinical safety blood samples will be forwarded to a central laboratory designated by the Sponsor for testing (see Section 6.5).

[7] A serum pregnancy test, if applicable, is required at Screening within 72 hours prior to dosing, and at the End of Treatment visit. In addition, serum- or urine pregnancy testing will be performed monthly (on Day 1 of each treatment cycle) while the patient receives study treatment, at the 30-day Safety Follow-up visit, and until 120 days after the last administration of study drug. (see Section 8.8.2).

[8] Blood samples for tumor markers, biomarkers, and ctDNA are only collected on Day 1 of Cycle 1 at pre-dose and every 8 weeks (two cycles) for the first six cycles (C3D1, C5D1, C7D1), once every 12 weeks (three cycles) thereafter (C10D1, C13D1, etc.), and at the End of Treatment visit. Blood samples for biomarkers and ctDNA will be collected only from patients enrolled after completion of the interim analysis, and subject to the granting of appropriate regulatory and IRB/IEC approval (see Section 6.7 and Appendix 3).

[9] Blood for sparse PK sampling is collected on C1D1, C1D15 and C3D1 at pre-dose (− 1 hour) and 6–8 hours post-dose. Blood for PK is collected on Day 1 of Cycles 2 and 4 at pre-dose (− 1 hour) (see Section 6.6 and Appendix 3). Blood for rich PK sampling for the PK/biomarker subgroup is collected on C1D1 and C2D1 pre-dose (− 1 hour), and 1 (± 5 minutes), 2 (± 5 minutes), 4 (± 15 minutes), 6 (± 15 minutes), 8 (± 30 minutes), 10 (± 30 minutes), 12 (± 30 minutes), and 24 hours after the daily dose of derazantinib (within 1 hour prior to the next dose), on C1D15 and C3D1, pre-dose (− 1 hour) and between 6 and 8 hours after the daily dose of derazantinib, and on C4D1 pre-dose (− 1 hour); the 10 and 12 h time-points are optional (see Appendix 3).

[10] In the rich PK sampling subset for urinary excretion: Urine for PK is collected on Day 1 of Cycle 2, starting from daily dose administration and until 24 h after dosing (immediately prior to the next dose) (see Appendix 3).

[11] The patient must test positive for *FGFR2* fusion (Substudy 1) or *FGFR2* mutation or amplification (Substudy 2). Details of FISH and NGS testing for this purpose are provided in Section 6.8, and summarised in Table 1 and Table 2.

[12] Tumor imaging assessments must be within 28 days prior to the first dose (see Section 6.9).

[13] Tumor measurement (CT/MRI scan of the chest, abdomen, and pelvis) and staging will be done every 8 weeks (two cycles) for the first six cycles (C3D1, C5D1, C7D1) and once every 12 weeks (three cycles) thereafter (C10D1, C13D1, etc.). Post-dose BS / WBMRI will be performed only if clinically indicated. If a scan shows CR/PR, a confirmation scan must be performed 4-5 weeks after the last scan was performed (see Section 6.9).

[14] Tumor measurement and staging will be performed at the End of Treatment visit only if the previous scan was not done within four weeks (28 days) prior to the End of Treatment visit or if the previous scan did not show radiographic disease progression (see Section 6.9).

[15] All medications taken within 30 days prior to the first dose are to be recorded.

[16] To avoid unnecessary waste of derazantinib capsules, in cases where treatment was interrupted and/or dose was reduced, the patient can continue dosing from the previously dispensed bottle until the next drug dispensing visit where re-supply is needed to maintain the protocol dosing regimen.

[17] Survival contact can be in person, via phone, or, where applicable, by checking regional/national death registries. All patients and/or family will be contacted at 3 month intervals (± 14 days) to record the patient status as Alive (date); Dead (date); Alive, but withdrew consent for further follow up; Lost to Follow Up. Survival updates may be made more often than every 3 months if the patient is seen at the investigational site for other reasons and for study level survival sweep(s) (see Section 5.6).

## Appendix 2 ECOG Performance Status

| ECOG Performance Status 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. |

## Appendix 3 Pharmacokinetic and pharmacodynamic sampling schedules

### BLOOD COLLECTION SCHEDULES FOR PHARMACOKINETIC ASSESSMENTS IN THE RICH PK SUBSET OF PATIENTS

- Cycle 1, Day 1 (FASTED): nine samples
  - One blood draw prior to the first dose of derazantinib (−1 hour)
  - One blood draw each, 1 (± 5 minutes), 2 (± 5 minutes), 4 (± 15 minutes), 6 (± 15minutes), 8 (± 30 minutes), 10 (± 30 minutes), 12 (± 30 minutes), and 24 hours after the first dose of derazantinib (within 1 hour prior to the next dose); the 10 and 12 hour time-points are optional.
- Cycle 1, Day 15: two samples
  - One blood draw before the daily dose of derazantinib (−1 hour)
  - One blood draw between 6 and 8 hours after the daily dose of derazantinib
- Cycle 2, Day 1: nine samples
  - One blood draw prior to the daily dose of derazantinib (−1 hour)
  - One blood draw each, 1 (± 5 minutes), 2 (± 5 minutes), 4 (± 15 minutes), 6 (± 15 minutes), 8 (±30 minutes), 10 (±30 minutes), 12 (±30 minutes), and 24 hours after the first dose of derazantinib (within 1 hour prior to the next dose); the 10 and 12 hour time-points are optional.
- Cycle 3, Day 1: two samples
  - One blood draw before the daily dose of derazantinib (−1 hour)
  - One blood draw between 6 and 8 hours after the daily dose of derazantinib
- Cycle 4, Day 1: one sample
  - One blood draw before the daily dose of derazantinib (−1 hour)

### URINE COLLECTION SCHEDULE FOR URINARY EXCRETION ASSESSMENTS IN THE SUBSET OF PATIENTS WITH URINE PK COLLECTION

- Cycle 2, Day 1: one pooled sample
  - Patient urinates normally (to waste) prior to administration
  - Starting from daily dose administration and until 24 h after the daily dose of derazantinib, urine is collected; at 24 h the patient voluntarily empties his/her bladder

**BLOOD COLLECTION SCHEDULES FOR PHARMACOKINETIC ASSESSMENTS IN ALL OTHER PATIENTS**

- Cycle 1, Day 1: two samples
  - One blood draw prior to the first dose of derazantinib (−1 hour)
  - One blood draw between 6 and 8 hours after the first dose of derazantinib
- Cycle 1, Day 15: two samples
  - One blood draw before the daily dose of derazantinib (−1 hour)
  - One blood draw between 6 and 8 hours after the daily dose of derazantinib
- Cycle 2, Day 1: one sample
  - One blood draw before the daily dose of derazantinib (−1 hour)
- Cycle 3, Day 1: two samples
  - One blood draw before the daily dose of derazantinib (−1 hour)
  - One blood draw between 6 and 8 hours after the daily dose of derazantinib
- Cycle 4, Day 1: one sample (−1 hour)
  - One blood draw before the daily dose of derazantinib

**BLOOD COLLECTION SCHEDULES FOR PHARMACODYNAMIC ASSESSMENTS***

- Cycle 1, Day 1: pre-dose sample
- Cycle 3, Day 1
- Cycle 5, Day 1
- Cycle 7, Day 1
- Cycle 10, Day 1 and every three cycles (12 weeks) thereafter
- End of Treatment

*Note: Blood samples for tumor markers will be collected for all enrolled patients. Blood samples for biomarkers and ctDNA will be collected only from patients enrolled after completion of the interim analysis, and subject to the granting of appropriate regulatory and IRB/IEC approval.

## Appendix 4 Examples of *in vivo* substrates, inhibitors, and inducers for specific CYP enzymes

Inhibitors can be classified by their potency, such as:

- *Strong inhibitor* being one that causes at least a 5-fold increase in the plasma area under the curve (AUC) values, or more than 80% decrease in clearance.
- *Moderate inhibitor* being one that causes at least a 2-fold increase in the plasma AUC values, or 50–80% decrease in clearance.
- *Weak inhibitor* being one that causes at least a 1.25-fold but less than 2-fold increase in the plasma AUC values, or 20–50% decrease in clearance.

| **Selected inducers, inhibitors, and substrates of CYP2C8** | | |
|---|---|---|
| **Substrates** | **Inhibitors** | **Inducers** |
| • Amodiaquine (anti-malarial)<br>• Cerivastatin (statin)<br>• Paclitaxel (anti-tumoral)<br>• Repaglinide (anti-diabetic)<br>• Sorafenib (anti-tumoral)<br>• Torsemide (diuretic) | **Strong**:<br>• Gemfibrozil (lipid lowering)<br>**Moderate**<br>• trimethoprim (antibiotic)<br>**Unspecified potency**:<br>• glitazones (anti-diabetic)<br>• montelukast (anti-asthmatic)<br>• quercetin (antioxidant, supplement) | • rifampin (antibiotic) |

| **Selected inducers, inhibitors, and substrates of CYP1A2** | | |
|---|---|---|
| **Substrates** | **Inhibitors** | **Inducers** |
| • many antidepressants<br>  ○ amitriptyline (tricyclic antidepressant)<br>  ○ clomipramine (tricyclic antidepressant)<br>  ○ imipramine (tricyclic antidepressant)<br>  ○ agomelatine<br>• some atypical antipsychotics<br>  ○ clozapine<br>  ○ olanzapine<br>• haloperidol (typical antipsychotic)<br>• caffeine (stimulant)<br>• ropivacaine (local anaesthetic)<br>• theophylline (xanthine, in respiratory diseases)<br>• zolmitriptan (serotonin receptor agonist)<br>• melatonin (antioxidant, sleep-inducer)<br>• tamoxifen (SERM)<br>• erlotinib (Tarceva, a tyrosine kinase inhibitor) | **Strong**:<br>• ciprofloxacin (fluoroquinolone bactericidal)<br>• many other fluoroquinolones (broad-spectrum antibiotics)<br>• fluvoxamine (SSRI antidepressant)<br>• verapamil (calcium channel blocker)<br>**Weak**<br>• cimetidine (H2-receptor antagonist)<br>**Unspecified potency**:<br>• amiodarone (antiarrhythmic agent)<br>• interferon (antiviral, antiseptic, antioncogenic)<br>• methoxsalen (in psoriasis)<br>• mibefradil (calcium channel blocker)<br>• **Some foods**<br>  ○ grapefruit juice (its bitter flavanone naringenin)<br>  ○ cumin<br>  ○ turmeric | • tobacco<br>• **Some foods**<br>  ○ broccoli<br>  ○ brussels sprouts<br>  ○ chargrilled meat<br>  ○ cauliflower<br>• insulin (in diabetes)<br>• methylcholanthrene (carcinogen)<br>• modafinil (eugeroic)<br>• nafcillin (beta-lactam antibiotic)<br>• beta-Naphthoflavone (chemopreventive)<br>• omeprazole (proton pump inhibitor) |

| Selected inducers, inhibitors, and substrates of CYP1A2 | | |
|---|---|---|
| **Substrates** | **Inhibitors** | **Inducers** |
| • cyclobenzaprine (muscle relaxant, depressant)<br>• estradiol (in hypoestrogenism)<br>• fluvoxamine (SSRI antidepressant)<br>• mexiletine (antiarrhythmic agent)<br>• naproxen (NSAID)<br>• ondansetron (5-HT3 antagonist)<br>• phenacetin (analgesic)<br>• paracetamol (analgesic, antipyretic)<br>• propranolol (beta blocker)<br>• riluzole (in amyotrophic lateral sclerosis)<br>• tacrine (parasympathomimetic)<br>• tizanidine (α-2 adrenergic agonist)<br>• verapamil (calcium channel blocker)<br>• warfarin (anticoagulant)<br>• zileuton (in asthma) | | |

| Selected inducers, inhibitors, and substrates of CYP2D6 | | |
|---|---|---|
| **Substrates**<br>**↑ = bioactivation by CYP2D6** | **Inhibitors** | **Inducers** |
| • All tricyclic antidepressants, e.g.<br>  ○ imipramine<br>  ○ amitriptyline<br>  ○ etc.<br>• Most SSRIs (antidepressant), e.g.<br>  ○ fluoxetine<br>  ○ paroxetine<br>  ○ fluvoxamine<br>• venlafaxine (SNRI antidepressant)<br>• mianserin (tetracyclic antidepressant)<br>• opioids<br>  ○ codeine↑ into morphine<br>  ○ tramadol↑<br>  ○ oxycodone<br>• antipsychotics, e.g.<br>  ○ haloperidol<br>  ○ risperidone<br>  ○ perphenazine<br>  ○ thioridazine<br>  ○ zuclopenthixol<br>  ○ iloperidone | **Strong**:<br>• SSRIs<br>  ○ fluoxetine<br>  ○ paroxetine<br>• bupropion (non-SSRI antidepressant)<br>• quinidine (class I antiarrhythmic agent)<br>• cinacalcet (calcimimetic)<br>• ritonavir (antiretroviral)<br>**Moderate**<br>• sertraline (SSRI)<br>• duloxetine (SNRI)<br>• terbinafine (antifungal)<br>**Weak**:<br>• buprenorphine (in opioid addiction)<br>• amiodarone (antiarrhythmic)<br>• cimetidine (H2-receptor antagonist)<br>**Unspecified potency**:<br>• antipsychotics<br>  ○ haloperidol | • dexamethasone (glucocorticoid)<br>• rifampicin (bactericidal)<br>**Strong**:<br>• glutethimid |

| Selected inducers, inhibitors, and substrates of CYP2D6 | | |
|---|---|---|
| **Substrates**<br>**↑ = bioactivation by CYP2D6** | **Inhibitors** | **Inducers** |
| ○ aripiprazole<br>○ chlorpromazine<br>○ levomepromazine<br>○ remoxipride<br>• minaprine (RIMA antidepressant)<br>• tamoxifen↑ (SERM)<br>• beta-blockers<br>○ metoprolol<br>○ timolol<br>○ alprenolol<br>○ carvedilol<br>○ bufuralol<br>○ nebivolol<br>○ propranolol<br>• debrisoquine (antihypertensive)<br>• Class I antiarrhythmics<br>○ flecainide<br>○ propafenone<br>○ encainide<br>○ mexiletine<br>○ lidocaine<br>○ sparteine<br>• ondansetron (antiemetic)<br>• donepezil (acetylcholinesterase inhibitor)<br>• phenformin (antidiabetic)<br>• tropisetron (5-HT3 receptor antagonist)<br>• amphetamine (in ADHD, narcolepsy)<br>• atomoxetine (in ADHD)<br>• chlorphenamine (antihistamine)<br>• dexfenfluramine (serotoninergic anorectic)<br>• dextromethorphan (antitussive) into psychoactive dextrorphan<br>• duloxetine (SNRI)<br>• metoclopramide (dopamine antagonist)<br>• Methoxyamphetamine<br>• perhexiline (antianginal agent)<br>• phenacetin (analgesic)<br>• promethazine (antihistamine antiemetic) | ○ perphenazine<br>○ thioridazine<br>○ zuclopenthixol<br>○ risperidone<br>○ chlorpromazine<br>• bicalutamide<br>• hyperforin (St. John's Wort)<br>• antihistamines (H1-receptor antagonists)<br>○ Promethazine<br>○ chlorphenamine<br>○ diphenhydramine<br>○ hydroxyzine<br>○ tripelennamine<br>• some SSRI antidepressants<br>○ citalopram<br>○ escitalopram<br>• clemastine (antihistamine and anticholinergic)<br>• celecoxib (NSAID)<br>• clomipramine (tricyclic antidepressant)<br>• cocaine (stimulant)<br>• doxorubicin (chemotherapeutic)<br>• metoclopramide (antiemetic, prokinetic)<br>• methadone (analgesic and anti-addictive)<br>• moclobemide (antidepressant)<br>• ranitidine (H2-receptor antagonist)<br>• doxepin (tricyclic antidepressant, anxiolytic)<br>• halofantrine (in malaria)<br>• levomepromazine (antipsychotic)<br>• mibefradil (calcium channel blocker)<br>• midodrine ($\alpha_1$ agonist)<br>• ticlopidine (antiplatelet) | |

Source: http://medicine.iupui.edu/clinpharm/ddis/table.aspx

## Appendix 5 Examples of *in vivo* substrates, inhibitors, and inducers of P-glycoprotein

| **Examples of *In Vivo* Substrates, Inhibitors, and Inducers of P-glycoprotein[1]** | | | |
|---|---|---|---|
| **Transporter** | **Substrates** | **Inhibitors[2]** | **Inducers[3]** |
| P-gp<br>(Gene *ABCB1*) | Aliskiren<br>ambrisentan<br>colchicine<br>dabigatran etexilate<br>digoxin<br>everolimus<br>fexofenadine<br>imatinib<br>lapatinib<br>maraviroc,<br>nilotinib<br>posaconazole<br>ranolazine<br>saxagliptin<br>sirolimus<br>sitagliptin<br>talinolol<br>tolvaptan<br>topotecan | Amiodarone<br>azithromycin[4]<br>captopril<br>carvedilol<br>clarithromycin<br>conivaptan<br>cyclosporine<br>diltiazem<br>dronedarone<br>erythromycin[5]<br>felodipine<br>itraconazole<br>ketoconazole[4]<br>lopinavir and ritonavir<br>quercetin[4]<br>quinidine<br>ranolazine<br>ticagrelor<br>verapamil | Avasimibe[6]<br>carbamazepine[7]<br>phenytoin<br>rifampin<br>St John's wort[8]<br>tipranavir/ritonavir |

Source: Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations (http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatory Information/Guidances/UCM292362.pdf ).

1 Not an exhaustive list. For an updated list, see the following link: http://www fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499 htm

2 Inhibitors listed for P-gp are those that showed >25% increase in digoxin AUC or otherwise indicated if substrate is other than digoxin

3 Inducers listed for P-gp are those that showed >20% decrease in digoxin AUC or otherwise indicated if substrate is other than digoxin

4 Inhibitors listed are those that showed >25% increase in fexofenadine AUC

5 Inhibitors listed are those that showed >25% increase in talinolol AUC

6 Not a marketed drug

7 Inducers listed are those that showed >20% decrease in fexofenadine AUC

8 Herbal product

## Appendix 6 Assessment of anti-tumor activity per RECIST v. 1.1

Assessment of tumor responses may be performed following the revised RECIST guidelines, version 1.1. Some of these definitions and criteria are highlighted below.

### Measurability of tumor baseline

- CT with intravenous (IV) contrast and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm.
- Standard imaging studies should be performed according to the imaging manual provided by the central imaging laboratory designated by the Sponsor.

### Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable

*Tumor lesions:* Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

*Measurable malignant lymph nodes:* To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

Non-measurable

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

**Special considerations regarding lesion measurability**

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

Bone lesions

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

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

Blastic bone lesions are non-measurable.

Cystic lesions

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

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

Lesions with prior local treatment

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression in the lesion.

## Specifications by methods of measurements

Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and NEVER more than 4 weeks before the beginning of the treatment.

Method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

*Clinical lesions:* Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g., skin (nevi) nodules). For the case of skin (nevi) lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

*Chest X-ray:* Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

*CT, MRI:* CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have a slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

## Tumor response evaluation

Assessment of overall tumor burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. In this study, only patients with measurable disease at baseline should be included in the study.

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

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

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

*Lymph nodes* merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As noted above, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

*A sum of the diameters* (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of the 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 of the diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

## Response criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

Evaluation of target lesions

- *Complete Response:* Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- *Partial Response:* At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- *Progressive Disease:* At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- *Stable Disease:* Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. In this study, the minimum duration for SD is defined as 8 weeks (± 2 days).

Special notes on the assessment of target lesions

*Lymph nodes*. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

*Target lesions that become 'too small to measure'*. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each Response Criteria subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs, it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned

(Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

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

Evaluation of non-target lesions

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

- *Complete Response:* Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
- *Non-CR/Non-PD:* Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- *Progressive Disease:* Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Special notes on the assessment of progression of non-target disease

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

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

Evaluation of new lesions

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

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

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

Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until the End of Treatment.

The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

Time point response

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

| **Time point response: Patients with target (+/– non-target) disease** | | | |
|---|---|---|---|
| **Target lesions** | **Non-target lesions** | **New lesions** | **Overall Response** |
| CR | CR | No | CR |
| CR | Non-CR/non-PD | No | PR |
| CR | Not evaluated | No | PR |
| PR | Non-PD or not all evaluated | No | PR |
| SD | Non-PD or not all evaluated | No | SD |
| Not all evaluated | Non-PD | No | NE |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable.

Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements is made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

Best overall response: all time points

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

*Best response determination in trials where confirmation of complete or partial response IS NOT required*: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be the best response, it must also meet the protocol specified minimum time from baseline of 8 weeks. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at the first assessment, PD at second the assessment, and does not meet the minimum duration for SD, the patient will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Special notes on response assessment

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

For patients with PR or CR, the Investigator should make every attempt to perform the confirmation scan 4 to 5 weeks after the last scan was performed. Radiographic disease progression must be confirmed by central radiology prior to treatment discontinuation if progression is seen on first or second post-treatment scan.

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

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

Frequency of tumor re-evaluation

In this study, tumor measurement will be conducted at baseline, and once every 8 weeks (every two cycles) from the day of the first dose for the first 6 months and once every 12 weeks (every three cycles) thereafter while the patient is on treatment or as clinically indicated until progression of disease, withdrawal of consent, or death. Tumor measurement will also be performed during the End of Treatment visit if it is not done within 28 days of the End of Treatment visit date or if prior scan did not show radiographic disease progression.

Baseline tumor assessments must be performed within three weeks (21 days) of the first dose of treatment.

All efforts must be made to ensure consistency between the baseline measurements and all subsequent measurements in reference to utilization of scanning methods, equipment, technique (including slice thickness and field of view), and the radiographic interpreter.

The radiological evaluation must include CT or MRI scanning of the chest, abdomen, and pelvis. Any additional suspected sites of disease should also be imaged. All evaluations must meet the standard of care for imaging of lesions in the respective organ(s).

All target and non-target sites are evaluated at each time point of tumor assessment.

**Confirmatory measurement/duration of response**

Confirmation

Confirmation of PR and CR is required 4–5 weeks after the initial scan showing PR or CR.

Duration of overall response

the duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

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

Duration of stable disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD). In this study, the minimum duration for SD is defined as 8 weeks (± 3 days).

## Appendix 7 Patient-reported outcomes guidelines

These guidelines assume that an appropriate person has been designated to facilitate the self-administration of the questionnaire.

**When and how should the questionnaire be administered?**

The QLQ-C30, QLQ-BIL21, EQ-5D, and the G-SET/HTI should be completed by the patient without assistance during his or her scheduled visits at the clinic. They should be administered at the start of the visit, before the patient sees the physician, and on day C1D1 prior to the first dose of study medication, so that any interaction between the patient and physician will not influence the patient's responses to the questionnaire. The questionnaires should also be administered before the patient is asked about adverse experiences and concurrent illnesses, again so that any discussions of health problems do not influence the patient's responses. The QLQ-C30, QLQ-BIL21, and EQ-5D are to be administered on Day 1 of the first cycle, every 8 weeks (two cycles) for the first six cycles, once every 12 weeks (three cycles) thereafter, and at the End of Treatment visit, and at the 30-day Safety Follow-up visit. The G-SET/HTI will be administered after 8 weeks (at Cycle 3 Day 1) and 16 weeks (at Cycle 5 Day 1).

A quiet place should be provided for the patient to complete the questionnaire. It is important that the patient completes the questionnaire alone, without any advice from family members or friends who may accompany them. On average, it takes less than 10 minutes to complete each questionnaire.

Patients must have basic fluency in the language of their country in order to complete the QLQ-C30, QLQ-BIL21, and EQ-5D. If a patient is not able to speak/read the language of his/her country, check if the patient has basic fluency in any of the languages in which the questionnaire is currently available and which has been approved by the sites IRB/IEC.

**How should the questionnaire be introduced?**

A sample script for introducing the questionnaire is given below.

'Your doctor would like to better understand how you feel, how well you are able to do your usual activities, and how you rate your health. To help us better understand these things about you, please complete the questionnaires about your health. The questionnaires are easy to fill out. The instructions are at the beginning of each questionnaire. You should read each question and then circle the appropriate number that matches your answer. Remember that this is not a test and there are no right or wrong answers. Choose the answer that best describes the way you feel. I will quickly review the questionnaire when you are finished to make sure that all of the questions have been answered. You should answer these questions by yourself. Your spouse or other family members should not help you when you answer the questionnaire. I will be nearby in case you want to ask me any questions. Please return the questionnaires to me when you have finished.'

**What to do if the patient asks for clarification?**

Some patients may ask the meaning of specific questions. If this happens, the staff member can assist the patient by re-reading the question for them verbatim. If the patient asks what something means, do not try to explain what the question means, but tactfully suggest that the patient use his/her own interpretation of the question. All patients should answer the questions based on what they think the questions mean, or the study results may be biased.

**Questionnaire completion**

When the patient returns the questionnaires, check that all of the questions have been answered. If the questionnaires are not complete, point out to the patient that some of the questions were not answered. If the patient does not quickly volunteer to answer these items, ask him/her whether she had any difficulty completing the questionnaire. If the patient says that he/she had trouble understanding a question, ask him/her why he/she had difficulty with that item. Re-read the question for him/her verbatim, but do not attempt to explain or reword the question, as explained before. If the patient is still unable to answer the question, accept the questionnaire as is.

Some patients may be confused by the response choices. They may want to respond with 'I don't know' or some other response choice that is not available. If this happens, try to help the patient choose one of the response categories by saying something like: 'I know that it may be difficult for you to choose an answer, but which of these answers do you think comes closest to the way that you are thinking or feeling?' If the patient still cannot select an answer, accept the questionnaire as is.

Occasionally, patients may not report having difficulty with a question or the response choices, but still may hesitate or refuse to answer an item or items. If this happens, accept the questionnaire as is.

If a patient asks for interpretation of his/her responses or asks for his/her scores on the questionnaire, tell him/her that you are not trained to score or interpret the questionnaire. Emphasize that their answers will be kept confidential.

**Completed questionnaires**

Thank the patient once he/she has completed the questionnaires and you have checked it for completeness.

## Appendix 8 *FGFR2* genetic aberrations eligible for enrollment in Substudy 2

NGS testing will be performed or commissioned by the respective study site using, as applicable, US FDA-approved and/or fully CE-marked industrial-scale assays. For enrollment of patients in the EU, assays must be either fully CE-marked or CE-marked for analytical performance, unless assays are exempt from this requirement by the IVDD (*Directive 98/79/EC*), i.e., manufactured and appropriately validated within health-institution laboratories for use in that environment and not subject to commercial transactions.

**Eligible *FGFR2* amplifications**

All levels of *FGFR2* amplifications.

**Eligible *FGFR2* mutations (small variants)**

Missense point mutations (substitutions), in-frame deletions, and insertions.

**The presence of the following *FGFR2* genetic aberrations is an Exclusion criterion even in the presence of an eligible mutation/amplification:**

- Any concurrent *FGFR2* translocations.

  *Note: If the NGS test used cannot identify FGFR2 translocations, a FISH test is mandatory to confirm that none are present.*
- Nonsense and frame-shift variants in exons 1–16, 17 (up to amino acid 761).
- Loss-of-function mutations H213Y, V248D, K517R, D530N, I642V, A648T, and R759X.
- Large deletions involving exons 11–17.
- Splice variants in introns 11–16.

## Appendix 9 Drugs with the potential to prolong QT and/or cause Torsades de Pointes

### ***Known*** risk of Torsades de Pointes*

| Generic name | Brand name | Generic name | Brand name |
|---|---|---|---|
| Aclarubicin | Aclacin and others | Ibogaine | None |
| Amiodarone | Cordarone and others | Ibutilide | Corvert |
| Anagrelide | Agrylin and others | Levofloxacin | Levaquin and others |
| Arsenic trioxide | Trisenox | Levomepromazine (methotrimeprazine) | Nosinan and others |
| Astemizole | Hismanal | Levomethadyl acetate | Orlaam |
| Azithromycin | Zithromax and others | Levosulpiride | Lesuride and others |
| Bepridil | Vascor | Mesoridazine | Serentil |
| Chloroquine | Aralen | Methadone | Dolophine and others |
| Chlorpromazine | Thorazine and others | Moxifloxacin | Avelox and others |
| Cilostazol | Pletal | Ondansetron | Zofran and others |
| Ciprofloxacin | Cipro and others | Oxaliplatin | Eloxatin |
| Cisapride | Propulsid | Papaverine HCl (Intra-coronary) | None |
| Citalopram | Celexa and others | Pentamidine | Pentam |
| Clarithromycin | Biaxin and others | Pimozide | Orap |
| Cocaine | Cocaine | Probucol | Lorelco |
| Disopyramide | Norpace | Procainamide | Pronestyl and others |
| Dofetilide | Tikosyn | Propofol | Diprivan and others |
| Domperidone | Motilium and others | Quinidine | Quinaglute and others |
| Donepezil | Aricept | Roxithromycin | Rulide and others |
| Dronedarone | Multaq | Sevoflurane | Ultane and others |
| Droperidol | Inapsine and others | Sotalol | Betapace and others |
| Erythromycin | E.E.S. and others | Sparfloxacin | Zagam |
| Escitalopram | Cipralex and others | Sulpiride | Dogmatil and others |
| Flecainide | Tambocor and others | Sultopride | Barnetil and others |
| Fluconazole | Diflucan and others | Terfenadine | Seldane |
| Gatifloxacin | Tequin | Terlipressin | Teripress and others |
| Grepafloxacin | Raxar | Terodiline | Micturin and others |
| Halofantrine | Halfan | Thioridazine | Mellaril and others |
| Haloperidol | Haldol and others | Vandetanib | Caprelsa |

* Source: CredibleMeds® (https://www.crediblemeds.org).

***Possible*** **risk of Torsades de Pointes***

| Generic name | Brand name | Generic name | Brand name |
|---|---|---|---|
| Abarelix | Plenaxis | Dexmedetomidine | Precedex and others |
| Alfuzosin | Uroxatral | Dextromethorphan/ Quinidine | Nuedexta |
| Apalutamide | Erleada | Dolasetron | Anzemet |
| Apomorphine | Apokyn and others | Efavirenz | Sustiva and others |
| Aripiprazole | Abilify and others | Eliglustat | Cerdelga |
| Artemether + Lumefantrine | Coartem | Encorafenib | Braftovi |
| Artenimol+piperaquine | Eurartesim | Epirubicin | Ellence and others |
| Asenapine | Saphris and others | Eribulin mesylate | Halaven |
| Atomoxetine | Strattera | Ezogabine (Retigabine) | Potiga and others |
| Bedaquiline | Sirturo | Felbamate | Felbatol |
| Bendamustine | Treanda and others | Fingolimod | Gilenya |
| Benperidol | Anquil and others | Fluorouracil (5-FU) | Adrucil and others |
| Betrixaban | Bevyxxa | Flupentixol | Depixol and others |
| Bortezomib | Velcade and others | Gemifloxacin | Factive |
| Bosutinib | Bosulif | Glasdegib | Daurismo |
| Buprenorphine | Butrans and others | Granisetron | Kytril and others |
| Cabozantinib | Cometriq | Hydrocodone - ER | Hysingla ER and others |
| Capecitabine | Xeloda | Iloperidone | Fanapt and others |
| Ceritinib | Zykadia | Imipramine (melipramine) | Tofranil |
| Clofazimine | Lamprene | Inotuzumab ozogamicin | Besponsa |
| Clomipramine | Anafranil | Isradipine | Dynacirc |
| Clotiapine | Entumine | Ketanserin | Sufrexal |
| Clozapine | Clozaril and others | Lacidipine | Lacipil and others |
| Crizotinib | Xalkori | Lapatinib | Tykerb and others |
| Cyamemazine (cyamepromazine) | Tercian | Lenvatinib | Lenvima |
| Dabrafenib | Tafinlar | Leuprolide | Lupron and others |
| Dasatinib | Sprycel | Lithium | Eskalith and others |
| Degarelix | Firmagon and others | Lopinavir and ritonavir | Kaletra and others |
| Delamanid | Deltyba | Maprotiline | Ludiomil and others |
| Desipramine | Pertofrane and others | Melperone | Bunil and others |
| Deutetrabenazine | Austedo | Memantine | Namenda XR and others |

*(Continued)*

* Source: CredibleMeds® (https://www.crediblemeds.org).

## ***Possible*** **risk of Torsades de Pointes (continued)***

| Generic name | Brand name | Generic name | Brand name |
|---|---|---|---|
| Midostaurin | Rydapt | Rilpivirine | Edurant and others |
| Mifepristone | Korlym and others | Risperidone | Risperdal |
| Mirabegron | Myrbetriq | Romidepsin | Istodax |
| Mirtazapine | Remeron | Saquinavir | Invirase(combo) |
| Moexipril/HCTZ | Uniretic and others | Sertindole | Serdolect and others |
| Necitumumab | Portrazza | Sorafenib | Nexavar |
| Nicardipine | Cardene | Sunitinib | Sutent |
| Nilotinib | Tasigna | Tacrolimus | Prograf and others |
| Norfloxacin | Noroxin and others | Tamoxifen | Nolvadex and others |
| Nortriptyline | Pamelor and others | Telavancin | Vibativ |
| Nusinersen | Spinraza | Telithromycin | Ketek |
| Ofloxacin | Floxin | Tetrabenazine | Nitoman and others |
| Osimertinib | Tagrisso | Tiapride | Tiapridal and others |
| Oxytocin | Pitocin and others | Tipiracil and Trifluridine | Lonsurf |
| Paliperidone | Invega and others | Tizanidine | Zanaflex and others |
| Palonosetron | Aloxi | Tolterodine | Detrol and others |
| Panobinostat | Farydak | Toremifene | Fareston |
| Pasireotide | Signifor | Tramadol | Crispin and others |
| Pazopanib | Votrient | Trimipramine | Surmontil and others |
| Perflutren lipid microspheres | Definity and others | Tropisetron | Navoban and others |
| Perphenazine | Trilafon and others | Valbenazine | Ingrezza |
| Pilsicainide | Sunrythm | Vardenafil | Levitra |
| Pimavanserin | Nuplazid | Vemurafenib | Zelboraf |
| Pipamperone | Dipiperon and others | Venlafaxine | Effexor and others |
| Primaquine phosphate | None | Vorinostat | Zolinza |
| Promethazine | Phenergan | Zotepine | Losizopilon and others |
| Prothipendyl | Dominal and others | Zuclopent(h)ixol | Cisordinol and others |
| Ribociclib | Kisqali | | |

* Source: CredibleMeds® (https://www.crediblemeds.org).

## ***Conditional*** **risk of Torsades de Pointes***

| Generic name | Brand name | Generic name | Brand name |
|---|---|---|---|
| Amantadine | Symmetrel and others | Ketoconazole | Nizoral and others |
| Amisulpride | Solian and others | Lansoprazole | Prevacid |
| Amitriptyline | Elavil and others | Loperamide | Imodium and many other OTC and Rx brands |
| Amphotericin B | Fungilin and others | Metoclopramide | Reglan and others |
| Amsacrine (acridinyl anisidide) | Amsidine | Metolazone | Zytanix and others |
| Atazanavir | Reyataz and others | Metronidazole | Flagyl and many others |
| Bendroflumethiazide or bendrofluazide | Aprinox and others | Nelfinavir | Viracept |
| Chloral hydrate | Aquachloral and others | Olanzapine | Zyprexa and others |
| Cimetidine | Tagamet and others | Omeprazole | Losec and others |
| Diphenhydramine | Benadryl and others | Pantoprazole | Protonix and others |
| Doxepin | Sinequan and others | Paroxetine | Paxil and others |
| Eperisone | Myonal and others | Piperacillin/Tazobactam | Tazosyn and Zosyn |
| Esomeprazole | Nexium and others | Posaconazole | Noxafil and others |
| Famotidine | Pepcid and others | Propafenone | Rythmol SR and others |
| Fluoxetine | Prozac and others | Quetiapine | Seroquel |
| Fluvoxamine | Faverin and others | Quinine sulfate | Qualaquin |
| Furosemide (frusemide) | Lasix and others | Ranolazine | Ranexa and others |
| Galantamine | Reminyl and others | Sertraline | Zoloft and others |
| Garenoxacin | Geninax | Solifenacin | Vesicare |
| Hydrochlorothiazide | Apo-Hydro and others | Telaprevir | Incivo and others |
| Hydroxychloroquine | Plaquenil and others | Torsemide (torasemide) | Demadex and others |
| Hydroxyzine | Atarax and others | Trazodone | Desyrel and others |
| Indapamide | Lozol and others | Voriconazole | VFend |
| Itraconazole | Sporanox and others | Ziprasidone | Geodon and others |
| Ivabradine | Procoralan and others | | |

* Source: CredibleMeds® (https://www.crediblemeds.org).

## Appendix 10 Sponsor's signature

| | |
|---|---|
| **Study Title:** | A pivotal study of derazantinib in patients with inoperable or advanced intrahepatic cholangiocarcinoma and *FGFR2* gene fusions or *FGFR2* gene mutations or amplifications |
| **Study Number:** | DZB-CS-301 |
| **Version / Date:** | Protocol Version 9.0 / 17 November 2020 |

## Appendix 11 Investigator's signature

| | |
|---|---|
| **Study Title:** | A pivotal study of derazantinib in patients with inoperable or advanced intrahepatic cholangiocarcinoma and *FGFR2* gene fusions or *FGFR2* gene mutations or amplifications |
| **Study Number:** | DZB-CS-301 |
| **Version / Date:** | Protocol Version 9.0 / 17 November 2020 |

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

**Signed by:** _____
Printed Name of Investigator

**Signature:** _____ **Date:** _____
Investigator DD/MMM/YYYY