CLINICAL STUDY PROTOCOL

Protocol DCC-2618-03-001 (INVICTUS)

A Phase 3, INterVentional, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of DCC-2618 In Patients with AdvanCed Gastrointestinal Stromal TUmorS who have Received Treatment with Prior Anticancer Therapies

NCT Number: 03353753

Document Date: Amendment 5 (30 October 2018)

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This study will be conducted according to the protocol and in compliance with Good Clinical Practice, the ethical principles stated in the Declaration of Helsinki, and other applicable regulatory requirements.

Study Sponsor:	Deciphera Pharmaceuticals, LLC
	Headquarters: 500 Totten Pond Road, 6th Floor Waltham, MA 02451 Phone: PI Fax: PI
	Research Facility: 643 Massachusetts St., Suite 200 Lawrence, KS 66044 Phone: PI Fax: PI
IND Number:	125279
EudraCT:	2017-002446-76
Document Version (Date):	Original (10 AUG 2017) Amendment 1 (07 NOV 2017) Amendment 2 (01 MAR 2018) Amendment 3 (22 MAR 2018) Amendment 4 (27 AUG 2018) Amendment 5 (30 OCT 2018)

SPONSOR SIGNATURE

PI

30 October 2018

Date

INVESTIGATOR STATEMENT

I understand that all documentation provided to me by Deciphera Pharmaceuticals, LLC or its designated representative(s) concerning this study that has not been published previously will be kept in the strictest confidence. This documentation includes the study protocol, Investigator brochure, case report forms, and other scientific data.

This study will not commence without the prior written approval of a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board. No changes will be made to the study protocol without the prior written approval of Deciphera Pharmaceuticals, LLC and the Institutional Review Board, except where necessary to eliminate an immediate hazard to the patient.

I have read, understood, and agree to abide by all the conditions and instructions contained in this protocol.

Investigator Name	Investigator Signature	Date

Name of Investigational Site

CLINICAL STUDY SYNOPSIS

Protocol Title:	A Phase 3, INterVentional, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of DCC-2618 In Patients with AdvanCed Gastrointestinal Stromal TUmorS who have Received Treatment with Prior Anticancer Therapies
Protocol Number:	DCC-2618-03-001
Protocol Name:	Invictus
Study Phase:	3
Study Centers:	Approximately 35 centers globally
Number of Patients Planned:	Approximately 120 patients (approximately 80 randomized to DCC-2618 and approximately 40 randomized to placebo)
Objectives:	**Primary Objectives:** • To assess the efficacy (progression-free survival [PFS]) of DCC-2618 by independent radiologic review in patients with advanced gastrointestinal stromal tumors (GIST) who have received prior therapies **Key Secondary Objectives:** • To assess objective response rate by independent radiologic review **Secondary Objectives:** • To assess other parameters of efficacy, including but not limited to time to progression (TTP) and overall survival (OS) • To assess the PD/PK relationship of DCC-2618 • To assess the robustness of efficacy using a sensitivity analysis • To assess improvement of disease-related symptoms and quality of life • To assess the safety of DCC-2618 **Exploratory Objectives:** • To assess the efficacy of DCC-2618 in patients after dose escalation to DCC-2618 150 mg twice daily (BID) • To characterize KIT and PDGFRA gene resistance mutations (and potentially other gene mutations) and their DCC-2618-driven longitudinal mutation allele frequency changes in plasma cell-free DNA (cfDNA) • To retrospectively correlate KIT and PDGFRA mutation/s and/or their frequency (as well as of potentially other gene mutations) in baseline cfDNA with clinical benefit • To understand potential tyrosine kinase inhibitor- (TKI) resistance mechanisms of GIST at time of progression • To determine concordance between KIT, PDGFRA, and other mutations in tumor and cfDNA at baseline • To assess healthcare utilization in patients with advanced GIST who have received approved therapies

Study Design:	This is a 2-arm, randomized, placebo-controlled, double-blind, international, multicenter study comparing the efficacy of DCC-2618+best supportive care (hereafter referred to as "DCC-2618") to placebo+best supportive care (hereafter referred to as "placebo") in patients with advanced gastrointestinal stromal tumors (GIST) who have received treatment with prior anticancer therapies. Prior anticancer therapies must include treatment with imatinib, sunitinib, and regorafenib (3 prior therapies). Up to 40% of enrolled patients may have received prior treatment with imatinib, sunitinib, regorafenib, and other drugs (≥4 prior therapies). Approximately 120 patients will be randomized in a 2:1 ratio to DCC-2618 150 mg once daily (QD) or placebo (see Figure 1). Randomization will be stratified by: • Patients who have received 3 prior anticancer treatments versus patients who have received ≥4 prior anticancer treatments o It should be noted that enrollment for patients who have received ≥4 prior anticancer treatments will be limited to 40% of the overall sample size. • Eastern Cooperative Oncology Group (ECOG) performance status (PS)=0 versus ECOG PS=1 or 2 The primary response for the study will be evaluated using the modified Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 - GIST-specific (hereafter referred to as "modified RECIST") based on independent radiologic review. Upon disease progression by modified RECIST based on independent radiologic review, study drug treatment will be unblinded. At that time: • **Patients randomized to DCC-2618 150 mg QD** will be given the option to: o continue DCC-2618 at an increased dose of 150 mg BID, or o continue treatment on study with the same dose if the Investigator feels the patient is receiving benefit from DCC-2618 or if dose escalation may not be tolerable for the patient (dose escalation is not permitted at a later time during the study), or o discontinue DCC-2618. • **Patients randomized to placebo** will be given the option to: o cross over to receive DCC-2618 150 mg QD, or o discontinue the study. **Patients randomized to placebo who cross over to receive DCC-2618 150 mg QD and have disease progression by modified RECIST based on Investigator assessment** will be given the option to: o continue DCC-2618 at an increased dose of 150 mg BID, or o continue treatment on study with the same DCC-2618 dose if the Investigator feels the patient is receiving benefit from DCC-2618 or if dose escalation may not be tolerable for the patient (dose escalation is not permitted at a later time during the study), or o discontinue DCC-2618.

Study Population: *Inclusion Criteria*	Patients must meet all of the following criteria to be eligible to enroll in the study: 1. Male or female patients ≥18 years of age at the time of informed consent 2. Histologic diagnosis of GIST 3. Patients must have progressed on imatinib, sunitinib, and regorafenib or have documented intolerance to any of these treatments despite dose modifications. 4. ECOG PS of 0 to 2 at screening. 5. Able to provide an archival tumor tissue sample if no anticancer therapy was administered since the sample was collected; otherwise, a fresh tumor tissue sample is required prior to the first dose of study drug. 6. Female patients of childbearing potential must have a negative serum beta-human chorionic gonadotrophin (β-hCG) pregnancy test at screening and a negative pregnancy test at Cycle 1 Day 1 prior to the first dose of study drug. 7. Patients of reproductive potential must agree to follow the contraception requirements outlined in Section 6.11.10. 8. The patient is capable of understanding and complying with the protocol and has signed the informed consent document. A signed informed consent form must be obtained before any study-specific procedures are performed. 9. At least 1 measurable lesion according to modified RECIST Version 1.1 (non-nodal lesions must be ≥1.0 cm in the long axis or ≥double the slide thickness in the long axis) within 21 days prior to the first dose of study drug. 10. Adequate organ function and bone marrow reserve as indicated by the following laboratory assessments performed at screening. • Absolute neutrophil count ≥1000/µL • Hemoglobin ≥8 g/dL • Platelet count ≥75,000/µL • Total bilirubin ≤1.5 x the upper limit of normal (ULN) • Aspartate transaminase and alanine transaminase ≤3 x ULN (≤5x ULN in the presence of hepatic metastases) • Serum creatinine ≤1.5 x ULN or creatinine clearance ≥50 mL/min based on either urine collection or Cockcroft Gault estimation. • Prothrombin time (PT), international normalized ratio (INR), and partial thromboplastin time ≤1.5 x ULN. Patients on a stable, maintenance regimen of anticoagulant therapy for at least 30 days prior to study drug administration may have PT/INR measurements >1.5 x ULN if, in the opinion of the Investigator, the patient is suitable for the study. An adequate rationale must be provided to the Sponsor prior to randomization. 11. Resolution of all toxicities from prior therapy to ≤Grade 1 (or baseline) within 1 week prior to the first dose of study drug (excluding alopecia and ≤Grade 3 clinically asymptomatic lipase, amylase, and creatine phosphokinase laboratory abnormalities).

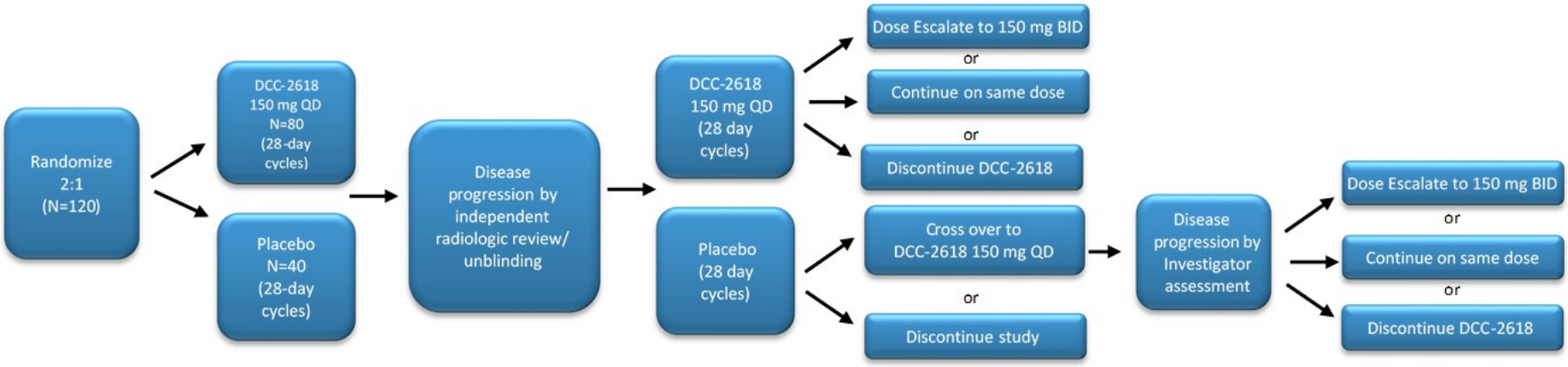
Exclusion Criteria	Patients meeting any of the following criteria will be excluded from the study: 1. Treatment with anticancer therapy, including investigational therapy, or investigational procedures within 14 days or 5 x the half-life (whichever is longer) prior to the first dose of study drug. For prior biological therapies, eg, monoclonal antibodies with a half-life longer than 3 days, the interval must be at least 28 days prior to the first dose of study drug. 2. Prior treatment with DCC-2618 3. Prior or concurrent malignancy whose natural history or treatment have the potential to interfere with the safety or efficacy assessment of DCC-2618. Patients receiving adjuvant cancer treatment are not eligible if those medications are potentially active against GIST or excluded per protocol (refer to Section 5.12.3). 4. Patient has known active central nervous system metastases. 5. New York Heart Association class II - IV heart disease, active ischemia or any other uncontrolled cardiac condition such as angina pectoris, clinically significant cardiac arrhythmia requiring therapy, uncontrolled hypertension or congestive heart failure. 6. Arterial thrombotic or embolic events such as cerebrovascular accident (including ischemic attacks) or hemoptysis within 6 months before the first dose of study drug. 7. Venous thrombotic events (eg, deep vein thrombosis) or pulmonary arterial events (eg, pulmonary embolism) within 3 months before the first dose of study drug. Patients with venous thrombotic events ≥3 months before the first dose of study drug on stable anticoagulation therapy are eligible. 8. 12-lead electrocardiogram (ECG) demonstrating QT interval corrected by Fridericia's formula >450 ms in males or >470 ms in females at screening or history of long QT interval corrected syndrome. 9. Left ventricular ejection fraction (LVEF) <50% at screening. 10. Use of proton-pump inhibitors within 4 days prior to the first dose of study drug. Other medications that increase gastric pH, ie, histamine H2 receptor antagonists and antacids may be taken provided they are not administered within 2 hours before or after administration of study drug. 11. Use of strong or moderate inhibitors and inducers of cytochrome P450 (CYP) 3A4, including certain herbal medications (eg, St. John's Wort) and consumption of grapefruit or grapefruit juice within 14 days or 5 x the half-life (whichever is longer) prior to the first dose of study drug. Please refer to the Indiana University Department of Medicine website (http://medicine.iupui.edu/clinpharm/ddis/main-table/) for guidance on medications that inhibit CYP3A4 enzymes. 12. Use of known substrates or inhibitors of breast cancer resistance protein (BCRP) transporters within 14 days or 5 x the half-life (whichever is longer) prior to the first dose of study drug. Please refer to the US Food and Drug Administration's (FDA) website

	(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm) for inhibitors and substrates. 13. Major surgeries (eg, abdominal laparotomy) within 4 weeks of the first dose of study drug. Following major surgeries, >4 weeks prior to the first dose of study drug, all surgical wounds must be healed and free of infection or dehiscence. 14. Any other clinically significant comorbidities, such as uncontrolled pulmonary disease, active infection, or any other condition, which in the judgment of the Investigator, could compromise compliance with the protocol, interfere with interpretation of the study results, or predispose the patient to safety risks. 15. Known human immunodeficiency virus or hepatitis C infection only if the patient is taking medications that are **excluded** per protocol (refer to Section 5.12.3), active hepatitis B, or active hepatitis C infection. 16. If female, the patient is pregnant or lactating. 17. Known allergy or hypersensitivity to any component of the investigational drug product. Patients with a history of Stevens-Johnson syndrome on a prior TKI are excluded. 18. Gastrointestinal abnormalities including but not limited to: • inability to take oral medication • malabsorption syndromes • requirement for intravenous alimentation. 19. Any active bleeding excluding hemorrhoidal or gum bleeding.
Study Drug:	DCC-2618 or matching placebo
Formulation:	Tablets
Dose:	150 mg QD or 0 mg QD
Route of Administration:	Oral
Study Endpoints:	**Primary Endpoint:** PFS based on independent radiologic review using modified RECIST (1; Appendix 17.1). Modified RECIST criteria includes: • No lymph nodes chosen as target lesions; enlarged lymph nodes followed as non-target lesions; • No bone lesions chosen as target lesions; • Positron emission tomography not acceptable for radiological evaluation; • A progressively growing new tumor nodule within a pre-existing tumor mass must meet the following criteria to be considered as unequivocal evidence of progression according to the modification of RECIST Version 1.1: (a) the lesion is at least 2 cm in size and definitively a new active GIST lesion (eg, enhancing with contrast or other criteria to rule out artefact); or (b) the lesion has to be expanding on at least 2 sequential imaging studies.

	Key Secondary Efficacy Endpoint: • Objective response rate (confirmed CR + confirmed PR) **Secondary Efficacy Endpoints:** • TTP based on independent radiologic review • OS • Time to best response • PFS based on Investigator assessment • Quality of life as determined by changes from baseline in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-item and EuroQol 5-Dimension 5-Level • Disease control rate (complete response [CR] + partial response [PR] + stable disease) at 12 weeks **Safety:** Treatment-emergent adverse events, adverse events of special interest, serious adverse events, dose reduction or discontinuation of study drug due to toxicity; and changes from baseline in ECOG PS, vital signs, ECGs, LVEF, dermatologic examinations, and clinical laboratory parameters. **Pharmacokinetics (PK):** • Correlation of PK with efficacy/safety • Population PK **Exploratory Endpoints:** **Efficacy:** • PFS by Investigator assessment after dose escalation to DCC-2618 150 mg BID **Biomarkers and Pharmacodynamics:** • Type and burden of mutations in plasma cfDNA • Treatment effect of DCC-2618 on cfDNA mutation allele frequency • Potential TKI-resistance mechanisms of GIST at time of progression • Concordance between KIT, PDGFRA and other mutations in tumor and cfDNA **Healthcare Utilization:** • Changes over time in healthcare utilization
Statistical Considerations:	• 2:1 randomization to DCC-2618 versus placebo • Primary endpoint is PFS based on independent radiologic review • Total sample size of approximately 120 patients (approximately 80 patients randomized to DCC-2618, and approximately 40 patients randomized to placebo) is expected to have at least 90% power assuming:

	• 9 months of recruitment and 6 additional months of follow-up (total study duration of 15 months) • A two-sided 5% significance level in testing the hypothesis of no difference between DCC-2618 and placebo. • Assumes a 15% dropout rate
Independent Data Monitoring Committee:	An independent data monitoring committee will monitor the safety data from this study on a periodic basis to help ensure the ongoing safety of study patients.
Duration of Study:	Patients will be treated on their assigned arm until they develop progressive disease, experience unacceptable toxicity, or withdraw consent. At the time of progressive disease by modified RECIST based on independent radiologic review and following unblinding of study drug treatment, patients receiving DCC-2618 will be allowed to dose escalate, continue on the same dose, or discontinue DCC-2618; and patients receiving placebo will be allowed to cross over to receive DCC-2618 and can dose escalate, continue on the same dose, or discontinue DCC-2618 upon further progression by Investigator assessment. Patients will be eligible to receive study drug for up to 2 years or until commercial supply of the drug is available. This will be extended by agreement between the Sponsor and Investigator for patients who exhibit evidence of clinical benefit and tolerability to the drug, and who adhere to the study procedures. The study will end following the last patient last visit.

Figure 1: Study Schema



NOTE: **Patients will be randomized ONLY at the start of the study**. Following disease progression by independent radiologic review/unblinding, the decision on how to proceed in the study will be by patient choice.

Table 1: Schedule of Assessments

Assessments / Procedures[1]	Screening[2]	Cycle 1		Cycles ≥2	EOT Visit (within 7 days after last dose)	Safety Follow Up	Overall Survival Follow Up[3] (±1 month)
Cycle Day	**-28 to -1**	**1 (Baseline)**	**15 (±1 day)**	**1 (±3 days)**		**30 Days Post Last Dose** (+5 days)	
Site Visit	X	X	X	X	X		
Phone Call						X	X
Informed Consent	X						
Inclusion/Exclusion Criteria	X						
Medical and Cancer History	X						
Prior Medications/Procedures[4]	X						
Pregnancy Test[5]	X	X		X	X		
Randomization[6]		X					
Clinical Laboratory Tests							
Hematology	X	X	X	X	X		
Serum Chemistries	X	X	X	X	X		
Coagulation[7]	X	X	X[7]	X	X		
Urinalysis[8]	X			X[8]	X		
Thyroid Testing (TSH, Free T3, Free T4)		X					
Physical Examination	X[9]	Examinations will be driven by clinical findings and/or patient complaints					
ECOG PS[10]	X	X	X	X	X		
Vital Signs and weight[11]	X	X	X	X	X		
Height	X						
12-lead ECG[12]	X	X		X	X		
Echocardiogram/MUGA[13]	X			X[13]	X		
Dermatologic Examination[14]	X			X[14]	X		
Ophthalmologic Examination[15]	X						
Adverse Event Reporting	Continuous from signing informed consent through safety follow up						
Concomitant Medications/Procedures	Continuous from on or after the first day of study drug dose through safety follow up						
EORTC-QLQ-C30[16]		X	X	X	X		
EQ-5D-5L[16]		X	X	X	X		
Healthcare Utilization[16]		X		X	X		
Study Drug Administration[17]		X	X	X			
Study Drug Dispensation[18]		X		X			

Assessments / Procedures[1]	Screening[2]	Cycle 1		Cycles ≥2	EOT Visit (within 7 days after last dose)	Safety Follow Up	Overall Survival Follow Up[3] (±1 month)
Cycle Day	-28 to -1	1 (Baseline)	15 (±1 day)	1 (±3 days)		30 Days Post Last Dose (+5 days)	
Study Drug Count			X	X	X		
PK Sampling[19]		X	X	X[19]	X		
Pharmacogenomics		X					
Tumor Tissue Sample[20]	X[20]						
Radiologic Imaging[21]	X[2]			X[21]	X		
Biomarker and PD Sampling (Plasma) [22]		X		X[22]	X		

CT=computed tomography; ECG=electrocardiogram; ECOG= Eastern Cooperative Oncology Group; EOT=End of treatment; EORTC-QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-item; EQ-5D-5L= EuroQol 5-Dimension 5-Level; MRI=magnetic resonance imaging, MUGA=multigated acquisition; PD=pharmacodynamic; PK=pharmacokinetic; PS=performance status; T3=triiodothyronine; T4=thyroxine; TSH=thyroid stimulating hormone

1. All assessments must be performed predose, unless otherwise specified. Additional unscheduled safety or efficacy assessments may be performed at any time as clinically indicated to determine the relevance of specific findings and/or the duration of events.
2. Screening must occur within 28 days prior to the first dose of study drug. Radiologic imaging must be performed within 21 days prior to the first dose of study drug. Radiologic imaging performed as standard of care prior to informed consent may be used as the Screening assessment as long as the imaging was performed within 21 days prior to the first dose of study drug.
3. All patients will be followed until withdrawal of consent or death from any cause. After the Safety Follow-Up Visit, patients will be contacted every 3 months (±1 month) to collect long-term survival data.
4. Any medication or non-drug therapy or procedure taken or performed within 30 days prior to screening and before the first dose of study drug.
5. A serum pregnancy test will be performed by a central laboratory at screening. Urine pregnancy tests will be performed at all other visits, except Cycle 1 Day 15. Serum pregnancy test may be performed instead of urine, if it is the site's standard practice and results are received prior to the patient being dosed in the clinic.
6. Randomization may occur up to 3 days prior to Cycle 1 Day 1.
7. Patients taking anticoagulants will also have a test at Cycle 1 Day 15. Monitoring of coagulation tests must be increased for as long as deemed clinically appropriate following a change in anticoagulant dose during the study.
8. Urinalysis testing will be performed at screening, Day 1 of Cycles 2, 3, and 4, and at the EOT Visit. If any result is abnormal, a microscopic analysis will be performed by the central laboratory.
9. A full physical examination as defined in Section 6.11.1 will be performed at screening.
10. ECOG PS may be performed post dose.
11. Vital sign measurements will be collected after the patient has been at rest (seated or supine position) for at least 5 minutes. In addition, weight will be collected at each visit.
12. All 12-lead ECGs will be performed after the patient has been at rest (supine or semi-recumbent position) for at least 15 minutes. The rest period begins after the placement of the ECG leads.
13. An echocardiogram or MUGA will only be performed at screening, Cycle 3 Day 1, and every third cycle thereafter (ie, Cycle 6, 9, 12, etc), and the EOT Visit, unless deemed clinically appropriate at other times. The same modality (echocardiogram or MUGA) must be used throughout the study. Echocardiogram or MUGA performed as standard of care prior to informed consent may be used as the Screening assessment as long as the echocardiogram or MUGA was performed within 28 days prior to the first dose of study drug.
14. All patients will be assessed by a consulting dermatologist for skin lesions, especially for squamous cell carcinoma, actinic keratosis, and keratoacanthomas, within 21 days prior to Cycle 1 Day 1 (baseline). Subsequently, patients will be assessed at Cycle 3 Day 1 and then every third cycle thereafter (ie, Cycle 6, 9, 12, etc.), at the EOT Visit, and as clinically indicated. Dermatologic exam that meets the protocol criteria that was performed as standard of care prior to informed consent may be used

as the Screening assessment as long as the exam was performed within 21 days prior to the first dose of study drug. Dermatologic examination may be performed up to 7 days prior to the corresponding study visit or post dose at the study visit. See Section 6.11.6 for further details.

15. Ophthalmologic examination will be performed at Screening and if clinically indicated during treatment with study drug. This examination does not have to be repeated if there is documentation of an examination that met protocol criteria within 28 days before the Screening Visit and after the last dose of previous anticancer treatment.
16. The EORTC QLQ-C30 and EQ-5D-5L questionnaires must be performed before the patient sees the Investigator or designee on the day of the scheduled visit. If the dermatologic examination or imaging assessments are completed within 7 days of the scheduled visit and the patient does not see the Investigator or designee, the questionnaires do not need to be completed on that day. The EORTC QLQ-C30 will be performed prior to the EQ-5D-5L, followed by the Healthcare Utilization Questionnaire. Questionnaires are collected via an electronic patient reported outcome system on provided tablet computers.
17. Patients should be instructed to take the study drug at approximately the same time each day. On days of planned study visits, patients will be informed to take the study drug at the study site after predose assessments are completed.
18. At the time of dose escalation, the patient must come to the site for study drug to be dispensed.
19. PK sampling will be performed at the following time points: Cycle 1 Day 1 predose and 6 hours after dosing, Cycle 1 Day 15 predose, and 2 and 6 hours after dosing, Cycle 2 Day 1 and Cycle 3 Day 1 predose, predose at every other cycle (eg, Cycle 5, 7, etc.), at disease progression, and at the EOT Visit. All predose samples must be collected within 60 minutes before dosing and all post dose samples must be collected ±30 minutes of the nominal time point. An unscheduled PK sample may be taken at the time of the onset of a new suspected, treatment-related adverse event when requested by the Sponsor.
20. Archival tumor tissue samples will be collected at screening as long as no anticancer therapy was administered since the sample was collected. Fresh tumor tissue sample will only be collected if a patient qualifies for the study based on all other entry criteria and archival tissue is not available or not collected after the last anticancer therapy.
    All Patients (optional): Additional tumor tissue samples may be collected for patients undergoing medical procedures including resection of metastases while on study or for patients that have disease progression if the patient consents and these samples will be used for further molecular testing of the cancer while treated with study drug.
21. CT scans of the pelvis, abdomen, and chest will be performed at screening (within 21 days of Cycle 1 Day 1). Subsequently, CT scans of the pelvis and abdomen will be performed every cycle through and including Cycle 4, and then every other cycle thereafter (ie, Cycle 6, 8, 10, etc.). CT scans of the chest will only be performed subsequently if the patient had lung metastases at screening or in case of lung symptoms (per the Investigator's discretion). Radiologic imaging may be performed up to 7 days prior to the corresponding study visit or post dose at the study visit. An initial indication of a partial or complete response based on investigator assessment must be confirmed ≥4 weeks later. MRI scans of the abdomen/pelvis and CT scan without contrast of the chest can be used for patients who are allergic to radiographic contrast media. Additionally, for patients whose local regulatory authority and/or ethics committee has not approved use of CT scans, MRIs may be used. Throughout the study, the same assessment technique must be used. Ultrasound scanning is not an acceptable substitute for CT scanning. See Section 6.10.1 for further details.
    Confirmation of No Disease Progression: If the independent radiologic reviewer confirms that there is no disease progression, the patient will continue to receive study drug unless there is a medical need (ie, rapid progression or clinical deterioration) that requires the study drug to be discontinued. If the Investigator determines progression based upon clinical deterioration, a scan must be performed and reviewed by the independent radiologic reviewer to determine if the patient progressed. The basis for determination of progression per clinical deterioration must be documented in the patient's source documents and electronic case report form.
    Disease Progression: Following confirmation of disease progression by modified Response Evaluation Criteria in Solid Tumors based on independent radiologic review, the patient's treatment assignment will be unblinded via the Interactive Response Technology system.
    - **Patients randomized to DCC-2618 150 mg QD** will be given the option to continue DCC-2618 at an increased dose of 150 mg twice daily, continue treatment on study with the same dose if the Investigator feels the patient is receiving benefit from DCC-2618 or if dose escalation may not be tolerable for the patient (dose escalation is not permitted at a later time during the study), or discontinue DCC-2618. At the time of dose escalation, the patient must come to the site for study drug to be dispensed.
    - **Patients randomized to placebo** will be given the option to cross over to receive DCC-2618 150 mg once or discontinue the study. Crossover patients must follow the schedule of assessments in Table 2.
22. Biomarker and PD plasma samples will be collected predose at Cycle 1 Day 1 (baseline), every other cycle (ie, Cycle 3, 5, 7, etc.), and at the EOT Visit.

Table 2: Schedule of Assessments for Crossover

Assessments / Procedures[1]	Cycle 1		Cycles ≥2	EOT Visit (within 7 days after last dose)	Safety Follow Up	Overall Survival Follow Up[3] (±1 month)
Cycle Day	**1**	**15 (±1 day)**	**1 (±3 days)**		**30 Days Post Last Dose** (+5 days)	
Site Visit	X	X	X	X		
Phone Call					X	X
Pregnancy Test[4]	X		X	X		
Clinical Laboratory Tests						
Hematology	X[2]	X	X	X		
Serum Chemistries	X[2]	X	X	X		
Coagulation[5]	X[2]	X[5]	X	X		
Urinalysis[6]	X[2]		X[6]	X		
Physical Examination	Examinations will be driven by clinical findings and/or patient complaints					
ECOG PS[7]	X[2]	X	X	X		
Vital Signs and weight[8]	X[2]	X	X	X		
12-lead ECG[9]	X[2]		X	X		
Echocardiogram/MUGA[10]	X[2]		X[10]	X		
Dermatologic Examination[11]	X[2]		X[11]	X		
Ophthalmologic Examination	Examinations will be performed if clinically indicated					
Adverse Event Reporting	Continuous through Safety Follow Up					
Concomitant Medications/Procedures	Continuous through Safety Follow Up					
EORTC-QLQ-C30[12]	X[2]	X	X	X		
EQ-5D-5L[12]	X[2]	X	X	X		
Healthcare Utilization[12]	X[2]		X	X		
Study Drug Administration[13]	X	X	X			
Study Drug Dispensation[14]	X		X			
Study Drug Count		X	X	X		
PK Sampling[15]	X	X	X[15]	X		
Tumor Tissue Sample (Optional)[16]	Additional tumor tissue samples may be collected through EOT					
Radiologic Imaging[17]			X[17]	X		
Biomarker and PD Sampling (Plasma)[18]	X[2]		X[18]	X		

CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC-QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-item; EOT=End of treatment; EQ-5D-5L= EuroQol 5-Dimension 5-Level; MRI=magnetic resonance imaging, MUGA=multigated acquisition; PD=pharmacodynamic; PK=pharmacokinetic; PS=performance status

1. All assessments must be performed predose, unless otherwise specified. Additional unscheduled safety or efficacy assessments may be performed at any time as clinically indicated to determine the relevance of specific findings and/or the duration of events.

2. If the patient had an assessment/procedure at the cycle visit when they progressed, then the assessment/procedure does not need to be performed at the Cycle 1 Day 1 Visit.
3. All patients will be followed until withdrawal of consent or death from any cause. After the Safety Follow-Up Visit, patients will be contacted every 3 months (±1 month) to collect long-term survival data.
4. Urine pregnancy tests will be performed at all visits, except Cycle 1 Day 15. Serum pregnancy test may be performed instead of urine, if it is the site's standard practice and results are received prior to the patient being dose in the clinic.
5. Patients taking anticoagulants will also have a test at Cycle 1 Day 15. Monitoring of coagulation tests must be increased for as long as deemed clinically appropriate following a change in anticoagulant dose during the study.
6. Urinalysis testing will be performed at Day 1 of Cycles 1, 2, 3 and 4, and at the EOT Visit. If any result is abnormal, a microscopic analysis will be performed by the central laboratory.
7. ECOG PS may be performed post dose.
8. Vital sign measurements will be collected after the patient has been at rest (seated or supine position) for at least 5 minutes. In addition, weight will be collected at each visit.
9. All 12-lead ECGs will be performed after the patient has been at rest (supine or semi-recumbent position) for at least 15 minutes. The rest period begins after the placement of the ECG leads.
10. An echocardiogram or MUGA will only be performed at Cycle 1 Day 1, Cycle 3 Day 1, every third cycle thereafter (ie, Cycle 6, 9, 12, etc.) and the EOT Visit, unless deemed clinically appropriate at other times. The same modality (echocardiogram or MUGA) must be used throughout the study.
11. All patients will be assessed, within 7 days of the scheduled visit or post dose on the day of the visit, by a consulting dermatologist for skin lesions, especially for squamous cell carcinoma, actinic keratosis, and keratoacanthomas at Cycle 1 Day 1, Cycle 3 Day 1 and then every third cycle thereafter (ie, Cycle 6, 9, 12, etc.), at the EOT Visit, and as clinically indicated. See Section 6.11.6 for further details. Note: If the patient had a recent dermatologic examination in the cycle when they progressed, then a dermatologic examination does not need to be performed at the Cycle 1 Day 1 visit.
12. The EORTC QLQ-C30 and EQ-5D-5L questionnaires must be performed before the patient sees the Investigator or designee on the day of the scheduled visit. If the dermatologic examination or imaging assessments are completed within 7 days of the scheduled visit and the patient does not see the Investigator or designee, the questionnaires do not need to be completed on that day. The EORTC QLQ-C30 will be performed prior to the EQ-5D-5L, followed by the Healthcare Utilization Questionnaire. Questionnaires are collected via an electronic patient reported outcome system on provided tablet computers.
13. Patients should be instructed to take study drug at approximately the same time each day. On days of planned study visits, patients will take the study drug at the study site after predose assessments are completed.
14. At the time of dose escalation, the patient must come to the site for study drug to be dispensed.
15. PK sampling will be performed at the following time points: Cycle 1 Day 1 predose and 6 hours after dosing, Cycle 1 Day 15 predose, and 2 and 6 hours after dosing, Cycle 2 Day 1 and Cycle 3 Day 1 predose, predose at every other cycle (eg, Cycle 5, 7, etc.), at disease progression, and at the EOT Visit. All predose samples must be collected within 60 minutes before dosing and all post dose samples must be collected ±30 minutes of the nominal time point. An unscheduled PK sample may be taken at the time of the onset of a new suspected, treatment-related adverse event when requested by the Sponsor.
16. **All Patients (optional):** Additional tumor tissue samples may be collected for patients undergoing medical procedures including resection of metastases while on study or for patients that have disease progression if the patient consents and these samples will be used for further molecular testing of the cancer while treated with study drug.
17. CT scans of the pelvis and abdomen will be performed every other cycle. CT scans of the chest will only be performed subsequently if the patient had lung metastases at screening or in case of lung symptoms (per the Investigator's discretion). Radiologic imaging may be performed up to 7 days prior to the corresponding study visit or post dose at the study visit. An initial indication of a partial or complete response based on investigator assessment must be confirmed ≥4 weeks later. MRI scans of the abdomen/pelvis and CT scan without contrast of the chest can be used for patients who are allergic to radiographic contrast media. Additionally, for patients whose local regulatory authority and/or ethics committee has not approved use of CT scans, MRIs may be used. Throughout the study, the same assessment technique must be used. Ultrasound scanning is not an acceptable substitute for CT scanning. See Section 6.10.1 for further details.
    Disease Progression: Following confirmation of disease progression by modified Response Evaluation Criteria in Solid Tumors based on Investigator review, patients will be given the option to continue DCC-2618 at an increased dose of 150 mg twice daily according to the rules in Section 5.2.1, continue DCC-2618 at the same dose if the Investigator feels the patient is receiving benefit from DCC-2618 or if dose escalation may not be tolerable for the patient (dose escalation is not permitted at a later time during the study), or discontinue DCC-2618. At the time of dose escalation, the patient must come to the site for study drug to be dispensed.
18. Biomarker and PD plasma samples will be collected predose at Cycle 1 Day 1, every other cycle (ie, Cycle 3, 5, 7, etc.), and at the EOT Visit.

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AML	Acute myeloid leukemia
ASM	Aggressive systemic mastocytosis
ATP	Adenosine triphosphate
AUC	Area under the concentration-time curve
AUC_{0-24}	Area under the concentration-time curve during 24 hours
β-hCG	Beta-human chorionic gonadotropin
BCRP	Breast cancer resistance protein
BID	Twice daily
BP	Blood pressure
BSEP	Bile salt export pump
cfDNA	Cell-free DNA
C_{max}	Maximum observed concentration
CMH	Cochran Mantel-Haenszel
CPK	Creatine phosphokinase
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DCR	Disease control rate
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EORTC	European Organisation for Research and Treatment of Cancer
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30 item
EOT	End of Treatment
ePRO	Electronic patient reported outcome
EQ-VAS	EuroQol visual analogue scale
EQ-5D-5L	EuroQol 5 Dimension 5 Level
ER	Efflux ratio
FDA	Food and Drug Administration
FDG-PET	^{18}F-Fluorodeoxyglucose positron emission tomography
FSH	Follicle stimulating hormone

fu	Fraction unbound
GBM	Glioblastoma multiforme
GCP	Good Clinical Practice
GI	Gastrointestinal
GIST	Gastrointestinal stromal tumor
GLP	Good Laboratory Practice
HCUQ	Healthcare Utilization Questionnaire
HDPE	High density polyethylene
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IC_{50}	Half maximal inhibitory concentration
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent To Treat
IV	Intravenous
KM	Kaplan-Meier
LVEF	Left ventricular ejection fraction
MAF	Mutation allele frequency
MDR1	Multidrug resistance protein 1
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MUGA	Multigated acquisition
NADPH	Nicotinamide adenine dinucleotide phosphate
NCI	National Cancer Institute
NGS	Next generation sequencing
NOAEL	No observed adverse effect level
OAT	Organic anion transporter
OCT	Organic cation transporter
ORR	Objective response rate
OS	Overall survival
PD	Pharmacodynamic(s)
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PMR	Partial metabolic response

PP	Per protocol
PR	Partial response
PS	Performance status
PT	Prothrombin time
QD	Once daily
QOL	Quality of life
QTc	QT interval corrected
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected by Fridericia's formula
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCC	Squamous cell carcinoma
SD	Stable disease
SM	Systemic mastocytosis
SOC	System organ class
SUSAR	Serious Unexpected Suspected Adverse Reaction
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
T_{max}	Time to maximum observed concentration
TSH	Thyroid Stimulating Hormone
TTP	Time to tumor progression
$T_{1/2}$	Half-life
T3	Triiodothyronine
T4	Thyroxine
ULN	Upper limit of normal
WCT PVG	Worldwide Clinical Trials Pharmacovigilance

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1. INTRODUCTION AND RATIONALE

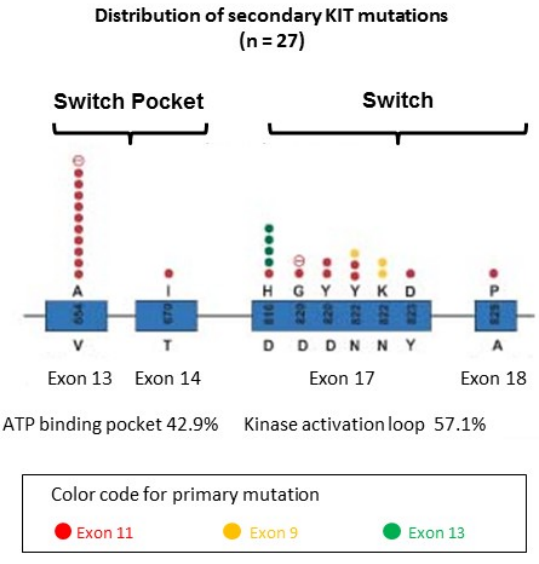
1.1. Introduction

Activating mutations in the receptor tyrosine kinases KIT or PDGFRA have been identified in multiple cancer types such as gastrointestinal stromal tumors (GIST), subsets of melanoma, testicular seminomas and acute myeloid leukemia (AML), and in myeloproliferative neoplasms such as systemic mastocytosis (SM) that include aggressive SM (ASM) and mast cell leukemia (2, 3, 4, 5, 6). In addition, aberrant wt KIT and/or PDGFRA overexpression is found in GIST, melanoma, AML, gliomas and neuroendocrine tumors (7, 8, 9, 10).

Most gastrointestinal stromal tumors are driven by activating mutations in KIT (~80%) or the related PDGFRA (~10%) receptor tyrosine kinases (1, 23). In GIST patients at presentation, mutations in the KIT gene are usually found in exon 9 or 11. Primary mutations in exon 11 disrupt the auto-inhibited form of the kinase, and those in exon 9 increase receptor dimerization. Both mechanisms cause ligand-independent receptor activation, which leads to uncontrolled cell growth and transformation. Several KIT-targeted therapies have been approved for the treatment of GIST, but there are limitations to their therapeutic success.

Upon treatment with targeted therapies, secondary resistance mutations in KIT usually arise in the catalytic domain of the kinase, and frequently these mutations map to the embedded conformational switch control mechanism that regulates KIT activity (Figure 2). Secondary mutations in KIT typically occur in exons 13 and 14 (near the adenosine triphosphate (ATP)-binding pocket) that sterically disrupt drug binding or conformationally activate KIT, and in the activation loop (conformation-controlling switch) encoded by exons 17 and 18 (11, 12). Activation loop mutations act by shifting the kinase into an activated conformation that is less amenable to drug binding by any of the approved therapies (13). Other diseases that have primary mutations in the KIT (or PDGFRA) activation loop include SM, AML, and PDGFRA-driven GIST (7, 14, 15).

Figure 2: Multiple Secondary KIT Mutations in Gastrointestinal Stromal Tumor Patients Span Exon Regions 13-18



Source: Liegl B, Kepten I, Le C, Zhu M, Demetri GD, Heinrich MC, et al. Heterogeneity of kinase inhibitor resistance mechanisms in GIST, J. Pathol. 2008 Sep;216(1):64-74.

Imatinib was the first KIT inhibitor approved as a therapy for advanced GIST in 2002 (16). Imatinib therapy is usually not curative in unresectable and/or metastatic disease with complete responses (CRs) seen in ~5% of patients and an objective response rate (ORR) of 68% (17). More than 80% of GIST patients will receive clinical benefit from imatinib monotherapy, but as development of imatinib-resistance is essentially inevitable, more than half will develop progressive disease by 2 years (18). Progression is largely due to secondary mutations in the KIT kinase domain that cause resistance to imatinib (12). Although imatinib is effective against exon 11 mutations in KIT, and has some efficacy against exon 9 mutations when the dose is increased to 800 mg, little to no response to imatinib is seen for other mutations in KIT and PDGFRA, particularly those that mediate the conformational dynamics of switch activation (18, 19).

Sunitinib was approved in 2006 as a second-line therapy for GIST patients who had disease progression on or intolerance to imatinib. Sunitinib has greater activity against exon 9 mutations compared to imatinib and less activity against exon 11 mutations (15, 18). Additionally, sunitinib shows activity against KIT exon 13 and 14 mutations, but only half the patients show benefit and median progression-free survival (PFS) is 5.5 months (18). Sunitinib is not effective against KIT exon 17/18 and PDGFRA exon 18 activation loop mutations.

Regorafenib was approved in 2013 as a third-line therapy for adult patients with metastatic and/or unresectable GIST who have had disease progression on or intolerance to imatinib and sunitinib treatment. In addition to being active against KIT exon 11 mutations, regorafenib is the only approved therapy with activity against a subset of exon 17 mutations in KIT and for patients who respond, PFS approaches 5 months. Some patients present with mutations in KIT that are not effectively treated by regorafenib, and additionally, other or multiple secondary mutations arise and cause resistance to therapy (12). Tumor heterogeneity has been found with multiple secondary mutations in KIT arising within an individual patient in different areas of 1 tumor or distinct sites of metastasis (12).

The complex heterogeneity of KIT mutations within individual patients is a major cause of resistance to therapy (12). A kinase inhibitor that could broadly inhibit clinically relevant KIT mutations or multiple mutations in KIT within an individual GIST patient could be of high therapeutic value in the treatment of refractory GIST patients. Importantly, determining whether such an inhibitor could delay development of resistance mutations within KIT is an important therapeutic objective with DCC-2618.

At present, there are no approved targeted therapies that broadly inhibit secondary drug-resistant mutations in GIST. Thus, a high medical need remains for developing kinase inhibitors that are effective against these mutant forms of KIT and PDGFRA.

1.2. Clinical Indications

DCC-2618, an inhibitor of KIT and PDGFRA kinases, is being developed for the treatment of patients with GIST, in addition to other advanced malignancies driven by proto-oncogene tyrosine-protein kinases. In addition to KIT and PDGFRA, the drug inhibits CSF1R (FMS), VEGFR2, and TIE2, which are less frequently documented to initiate tumor development.

Gastrointestinal stromal tumors represent the most common form of sarcoma, a relatively rare subset of cancers arising from mesenchymal cells in the body (20). Adult GIST occurs with an incidence rate of ~3,000-6,000 new cases per year in the US (21, 22, 23), generally presents around age 50-70, and occurs in men and women at similar rates (24). Surgery is the primary treatment for localized GIST and can be curative, though local and/or distant recurrence occurs in more than half of patients (25). For metastatic or unresectable GIST,

which is present in about half of patients at diagnosis, radiotherapy and traditional chemotherapy are not effective (20, 25). The era of targeted cancer therapies has ushered in several new effective treatments for metastatic and recurrent GIST, though CRs are rarely achieved (20). Resistance to therapy occurs in a large majority of patients within a few months to years depending on treatment (21), similar to that observed in other cancers successfully treated with targeted therapies.

1.3. Study Drug

DCC-2618 is a novel, oral inhibitor of KIT kinase and PDGFRA kinases, developed by Deciphera Pharmaceuticals, LLC (hereafter referred to as the "Sponsor"), using its proprietary kinase switch control inhibitor technology platform. DCC-2618 comprehensively and potently inhibits a broad range of primary and secondary mutants of KIT and PDGFRA kinases, including KIT primary mutations in exons 9 and 11 and secondary resistance mutations in exon 13 and 14 of the KIT ATP binding/switch pocket region and primary or secondary mutations in exons 17 and 18 of the activation loop conformation-controlling switch region. DCC-2618 also inhibits the PDGFRA primary exon 18 mutation D842V in the conformation-controlling switch region and exon 12 mutations in the auxiliary inhibitory switch. DCC-2618 exhibits this broad profile of mutant KIT/PDGFRA inhibition by binding as an advanced Type II kinase inhibitor that penetrates the embedded KIT/PDGFRA switch pockets.

1.3.1. Nonclinical Experience

Please refer to the Investigator's Brochure (IB) for a more detailed summary of the nonclinical experience with DCC-2618.

1.3.1.1. Pharmacology

DCC-2618, and its active metabolite, DP-5439, were evaluated in vitro in recombinant kinase assays and in cellular assays with GIST cell lines from treatment-resistant patients, AML and mastocytosis cell lines, or cell lines transfected with KIT or PDGFRA mutants. These studies provided a comprehensive profile of inhibition versus clinically relevant KIT and PDGFRA mutations that cause either de facto refractoriness to existing therapies or resistance to existing therapies. Results from evaluation in cancer cell lines guided further evaluation of DCC-2618 in refractory/resistant in vivo xenograft models.

A variety of cancer model systems were employed to evaluate the pharmacology of DCC-2618 in vivo, including the evaluation of efficacy in human tumor xenografts in nude mice and pharmacokinetic (PK)/pharmacodynamic (PD) studies in tumor-bearing mice to evaluate exposures required for durable mutant KIT inhibition in vivo.

In vivo, DCC-2618 exhibited potent anti-tumor effects in mutant KIT GIST models. Additionally, DCC-2618 showed potent inhibition of KIT phosphorylation in GIST models.

In a PK/PD study performed in a human GIST xenograft mouse model, a single oral dose of 50 mg/kg resulted in a DCC-2618 exposure (area under the concentration × time curve from 0 to 24 hours [$AUC_{0\text{-}24hr}$]) of 2500 ng•h/mL (5000 ng•h/mL when active metabolite DP-5439 is included) that led to 69-88% inhibition of KIT kinase in vivo through 8-hours post dose and ~40% inhibition at 12-hours post dose. This exposure led to 90% inhibition of tumor growth in the GIST T1 model when dosed at 50 mg/kg twice daily (BID; 10,000 ng•h/mL daily exposure) in a multiple-dose efficacy study. This PK/PD derived exposure was used to guide identification of toxicology formulations capable of achieving exposures as multiples of this durable inhibition of KIT in vivo.

Metabolite identification studies in hepatocytes revealed that the major metabolic pathway of DCC-2618 is N-demethylation to form an active metabolite known as DP-5439. In preclinical animal studies, significant fractions of DP-5439 were measured in mouse, rat, and dog plasma in preclinical studies. The metabolite was produced most extensively in mice and the PK parameters suggest that mice may be exposed to an approximately equal amount of DCC-2618 and DP-5439 when measured as $AUC_{0\text{-}24hr}$. The total active drug exposure in mice ($AUC_{0\text{-}24hr}$), as measured by the combined exposure of DCC-2618 and metabolite DP-5439, is therefore regarded as 5000 ng•h/mL following a single oral 50 mg dose or 10,000 ng•h/mL after a 50 mg/kg BID administration, a value which will be referenced in the analysis of nonclinical safety studies. Metabolite DP-5439 has been shown to be formed in the Phase 1 dose-escalation study. At clinically effective doses the exposure to metabolite is greater than exposure to parent DCC-2618.

DCC-2618 was selected for clinical development based on the efficacy and tolerability observed in these model systems.

1.3.1.1.1. Safety Pharmacology

DCC-2618 exhibits negligible binding to human ether-à-go-go related gene potassium channel components.

DCC-2618 given at 15, 60, or 300 mg/kg had no effect on any component of the modified Irwin battery of behavioral testing at any measured time point in rats. DCC-2618 given at 15, 60, or 300 mg/kg mildly decreased tidal volume by 10% at 15 mg/kg and up to 17% at 300 mg/kg in rats. The observed changes in tidal volume were not considered physiologically important because they were transient and of small magnitude.

Cardiovascular safety was assessed by electrocardiogram (ECG), blood pressure (BP), and troponin I measurements in the dog 4-week repeat dose toxicology study. No significant effects on blood pressure, heart rate, ECG intervals, or troponin I levels were noted. In a stand-alone cardiovascular safety study in Beagle dogs, single doses of DCC-2618 resulted in increased diastolic pressure and mean arterial pressure (2-6 hours post dose) that were generally correlative with the anticipated time to reach the maximum plasma concentration (T_{max}). Diastolic pressures were higher (12, 12, and 17%) than control at 7, 20, and 75 mg/kg, respectively. DCC-2618-related increases in mean arterial pressure were higher (up to 12, 10, and 14 mmHg) than control at 7, 20, and 75 mg/kg, respectively. There were no changes to systolic pressure or arterial pulse pressure.

Increases in heart rate and lower QT- and PR-intervals (likely secondary to changes in heart rate) were seen at 9 to 19-hours post dose during the dark phase of the study. There were no changes in corrected QT interval (QTc) values. Heart rate values were elevated throughout the dark phase with maximal differences occurring between 13 and 17-hours post dose when heart rates were 45%, 70%, and 129% higher than concurrent controls at 7, 20, and 75 mg/kg, respectively. The mechanism of these changes is not understood; BP and heart rate are being closely monitored in clinical studies. The magnitude of BP and heart rate changes was considered noteworthy, but not to represent severe toxicity.

1.3.1.2. Pharmacokinetics and Absorption, Distribution, Metabolism, and Excretion Profile

In vitro studies were performed to characterize the absorption, distribution, metabolism, and excretion properties of DCC-2618 and metabolite DP-5439 in human and other mammalian species relevant to drug development. In vivo PK studies (both oral and intravenous [IV] routes) were conducted in rodents (mice, rats) and non-rodents (dogs, cynomolgus monkeys).

DCC-2618 exhibited oral bioavailability in all species, confirming the potential for development as an oral therapeutic agent.

Total exposures ($AUC_{0\text{-}24hr}$) for DCC-2618 achieved in dogs and rats were 1.9-2.6 × the target area under the curve (AUC) of 10,000 ng•h/mL for DCC-2618 and metabolite DP-5439 in the murine GIST efficacy model. The elimination half-life ($T_{1/2}$) after a single IV dose was comparable in dogs (2.7 hours) and rats (2.0 hours).

Metabolite identification studies demonstrated that all observed human metabolites were also detected in the Sprague-Dawley rat and/or Beagle dog, supporting the relevance of these species for toxicology studies. The major metabolite observed in all species of hepatocytes is the N-desmethyl metabolite (DP-5439) and it was determined that DP-5439 inhibited wild type and mutant KIT and PDGFRA with potency comparable to DCC-2618. In a broad range of 19 single and double-mutant KIT assays performed in transfected Chinese Hamster Ovary cells, DCC-2618 inhibited mutant KIT phosphorylation with half maximal inhibitory concentration (IC_{50}) values ranging from 6 nM to 221 nM. Similarly, the metabolite DP-5439 inhibited mutant KIT phosphorylation in these assays with IC_{50} values ranging from 21 nM to 191 nM.

The in vitro metabolism of DCC-2618 and active metabolite DP-5439 by human liver microsomes was studied to determine which human cytochrome P450 (CYP) enzymes contribute to the metabolism of DCC-2618. The metabolism of DCC-2618 was found to be dependent on the presence of nicotinamide adenine dinucleotide phosphate (NADPH), reduced form. Blocking the metabolism of DCC-2618 in cultured human liver microsomes by the co-administration of specific direct-acting or metabolism-dependent CYP inhibitors revealed that CYP3A4/5 is the major metabolizer of DCC-2618 (ketoconazole, 63% inhibition; troleandomycin, 79% inhibition); CYP2C8 (gemfibrozil glucoronide, 24% inhibition) and CYP2D6 (quinidine, 26% inhibition) were implicated as only minor metabolizers. In recombinant human CYP enzyme preparations, however, CYP2D6 and CYP2C8 were also found to be strong metabolizers of DCC-2618. Inhibition of DP-5439 metabolism was observed in microsomal incubations with direct-acting inhibitor ketoconazole (CYP3A4/5, 72% inhibition), and with metabolism-dependent inhibitors gemfibrozil glucuronide (CYP2C8, 59% inhibition), tienilic acid (CYP2C9, 25% inhibition), esomeprazole (CYP2C19, 31% inhibition), paroxetine (CYP2D6, 42% inhibition), diethyldithiocarbamate (CYP2E1, 50% inhibition) and troleandomycin (CYP3A4/5, 100% inhibition). Incubations of DP-5439 with other direct or metabolism-dependent inhibitors evaluated resulted in less than 14% inhibition. This study revealed that CYP3A4/5 is the major metabolizer of DP-5439, but that significant metabolism is also possible by CYP2C8, CYP2E1, and CYP2D6. DCC-2618 did not appreciably inhibit CYP3A4, CYP1A2, or CYP2B6 in in vitro metabolism studies. DCC-2618 inhibited CYP2C8, CYP2C9, CYP2C19, and CYP2D6 with IC_{50} values ranging from 0.12 to 1.8 μM. DCC-2618 exhibited little or no evidence of time- or metabolism-dependent inhibition of any of the 7 major CYP enzymes evaluated.

Similarly, metabolite DP-5439 was also found to inhibit CYP2C8, CYP2C9, CYP2C19, and CYP2D6 with IC_{50} values ranging from 0.30 to 2.0 μM. DP-5439 did not appreciably inhibit CYP3A4, CYP1A2 or CYP2B6 in a direct manner. After a 30-minute pre-incubation with pooled human liver microsomes in the presence of NADPH, however, DP-5439 demonstrated evidence of metabolism-dependent (time-dependent and NADPH-dependent) inhibition of CYP3A4/5-mediated testosterone 6β-hydroxylation. The inhibition observed in the presence of 7.0 μM DP-5439 increased 41% after pre-incubation. There was little or no evidence of metabolism-dependent (time- and NADPH-dependent) inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 by DP-5439. DCC-2618 and DP-5439

exhibit potential for DDIs with other agents dependent on CYP2C8, CYP2C9, CYP2C19, or CYP2D6 for their metabolism.

In the presence of 10 µM DCC-2618 or 7 µM DP-5439, organic anion transporter (OAT) OAT1, OAT3, organic cation transporter (OCT) OCT1, and OCT2 were slightly to moderately inhibited by ≤55%. OATP1B3 was inhibited 78% by DCC-2618, whereas OATP1B1 was inhibited 73% by DP-5439 (Table 3).

DCC-2618 and DP-5439 were found to inhibit the breast cancer resistance protein (BCRP) efflux transporter in an in vitro vesicular transport assay with IC_{50} values of 0.04 µM and 1.26 µM, respectively. While DCC-2618 was not a substrate for the BCRP transporter (efflux ratio [ER] 2.36), the metabolite DP-5439 exhibited significant substrate activity (ER 85.0), indicating the potential for drug-metabolite interactions wherein DCC-2618 is a potential perpetrator (BCRP IC_{50} 0.04 µM) and metabolite DP-5439 is a potential victim (BCRP ER 85.0) of drug-drug interaction. DCC-2618 also has the potential for drug-drug-interaction with other agents that are substrates or inhibitors of the BCRP efflux transporter.

DCC-2618 and DP-5439 were moderate to weak inhibitors of the Multidrug resistance protein 1 (MDR1) efflux transporter, exhibiting IC_{50} values of 1.95 µM and >7 µM, respectively. While DCC-2618 was a moderate substrate for the MDR1 transporter (ER 12.9), the metabolite DP-5439 exhibited significant substrate activity (ER 72.4), indicating low to moderate potential for drug-metabolite interactions wherein DCC-2618 is a potential perpetrator (MDR1 IC_{50} 1.95 µM) and metabolite DP-5439 is a potential victim (MDR1 ER 72.4) of drug-drug-interaction (Table 3).

Table 3: Transporter Interactions of DCC-2618 and Metabolite DP-5439

	Inhibition of Transporter		Substrate of Transporter	
	DCC-2618	**DP-5439**	**DCC-2618**	**DP-5439**
BCRP	IC_{50} 0.040 µM	IC_{50} 1.26 µM	ER 2.36	ER 85.0
MDR1	IC_{50} 1.95 µM	IC_{50} >7 µM	ER 12.9	ER 72.4
BSEP	IC_{50} 1.63 µM	54% inhibition @ 7 µM	NT	ER <2
OATP1B1	32% inhibition @ 10 µM	73% inhibition @ 7 µM	NT	ER <2
OATP1B3	78% inhibition @ 10 µM	43% inhibition @ 7 µM	NT	ER <2
OCT1	30% inhibition @ 10 µM	NT	NT	NT
OCT2	55% inhibition @ 10 µM	6% inhibition @ 10 µM	NT	ER<2
OAT1, OAT3,	≤15% inhibition @ 10 µM	≤13% inhibition @ 7 µM	NT	ER <2

IC_{50}=half maximal inhibitory concentration; ER=efflux ratio; NT=not tested

1.3.1.3. Toxicology

The toxicity profile of DCC-2618 was evaluated in vitro in the bacterial mutagenicity assay and in vivo in nude mice, Sprague-Dawley rats and Beagle dogs. There was no evidence of bacterial mutagenicity up to the maximum tested concentration of 3000 µg/plate (concentration resulting in precipitation), with or without metabolic activation, in a non-Good Laboratory Practice (GLP) compliant assessment.

A pivotal, GLP-compliant 4-week oral study was conducted in rats at 0, 15, 60, and 300 mg/kg/day DCC-2618. Recovery animals were held for an additional 4 weeks following the dosing phase. There were no drug related deaths or adverse clinical observations in this study. A higher prevalence of thinning hair coat was noted at 300 mg/kg/day. A decrease in body weight and food consumption was seen in DCC-2618 treated animals. Body weight and food consumption changes reversed during the recovery phase, and neither had any effect on

the animals' overall body condition. Several minor clinical pathology findings were observed on Day 29. These changes were of small magnitude, lacked microscopic correlates, exhibited reversibility at the end of the recovery phase, and were not considered adverse. DCC-2618 related increased lung weights (15% to 33%) were noted in males given 300 mg/kg/day and females given ≥15 mg/kg/day. There were no correlating microscopic changes and the lung weight increases partially reversed during the recovery phase. Microscopic changes were limited to the non-glandular stomach (diffuse hyperplasia/hyperkeratosis) of rats given ≥60 mg/kg/day and the change partially reversed during the recovery phase. Since humans do not have this anatomic feature, the changes have no relevance to humans. Based on these results, 300 mg/kg/day was the no observed adverse effect level (NOAEL) after 4 weeks of dosing.

A pivotal, GLP compliant 4-week oral study was conducted in Beagle dog at 0, 7, 20, and 75 mg/kg/day. Recovery animals were held for an additional 4 weeks following the dosing phase. Dosing was suspended in several animals at 20 and 75 mg/kg/day during Week 2 or 3 due to DCC-2618-related adverse clinical observations. Three males given 75 mg/kg/day were sacrificed on Day 13, and 7 additional animals at both the 20 mg/kg dose (2 males and 2 females) and the 75 mg/kg dose (3 females) underwent early sacrifice during Week 4, due to DCC-2618-related adverse clinical observations. Clinical observations in these animals included erythema of feet, inside of ears, muzzle, periorbital area, and ventral thorax, and thinning of cranial hair coat. Some dogs also exhibited dry and flaky skin, otitis, erythematous external ear canals, excessive salivation, emesis, and non-formed/liquid feces. In dogs administered 7 mg/kg/day, skin changes were of lesser severity and judged not to be adverse. The skin lesions at 20 and 75 mg/kg/day were partially or completely resolved during the recovery phase. Decreased body weights were noted in males given 20 or 75 mg/kg/day. Animals at 7 mg/kg/day had small changes in body weight that were not considered adverse. No alterations in blood pressure or ECG intervals were noted at any dose of DCC-2618. Mild hematology, clinical biochemistry, and/or coagulation findings occurred in animals given ≥20 mg/kg/day and all changes exhibited evidence of reversibility by the end of the recovery phase. Troponin I levels in DCC-2618-treated animals were unaffected by drug treatment. Microscopic findings of hyperkeratosis, cytoplasmic rarefaction of hepatocytes consistent with increased glycogen, decreased lymphocytes in lymphoid tissues, and one instance of an intra-epidermal pustule were seen at ≥20 mg/kg/day. The only test article-related microscopic finding at the recovery sacrifice was minimal cytoplasmic rarefaction of liver cells in some animals given 75 mg/kg/day, indicating partial recovery of this finding.

Based on these results, the NOAEL is 7 mg/kg/day. This dose also is considered the highest non-severely toxic dose.

1.3.2. Clinical Experience

There is 1 ongoing clinical study with DCC-2618, Clinical Study DCC-2618-01-001. This is an open-label, first-in-human, dose-escalation study in patients with advanced malignancies with a molecular rationale for activity. This study has 2 parts: (1) Dose-Escalation Phase and (2) Expansion Phase.

In the Escalation Phase, sequentially increasing dose levels of oral DCC-2618 dosed BID in repeated 28-day cycles are being evaluated for safety based on pharmacologically guided 3+3 escalation rules until a maximum tolerated dose has been identified or a recommended expansion dose/regimen(s) is declared. Sequentially increasing dose levels of oral DCC-2618 dosed once daily (QD) were introduced based on the suspected long plasma half-life of an active metabolite (30-60 hours), that support a QD dosing regimen.

Upon determination of the single-agent recommended Phase 2 dose (RP2D) in the Escalation Phase, patients will be enrolled into the Expansion Phase of the study. Expansion will enroll several cohorts including patients with KIT- and PDGFRA-mutant GIST, SM and other hematologic malignancies, malignant gliomas, and other solid tumors.

As of 28 July 2017, 70 patients have been enrolled as follows: 57 patients with advanced GIST cancer, and 13 patients with non-GIST.

The clinical data represent a broad patient population with GIST patients having received various numbers of prior therapy ranging from a single prior therapy to patients who have received seven prior therapies.

In the Escalation Phase, 9 cohorts have been evaluated: 20 mg BID, 30 mg BID, 50 mg BID, 100 mg BID, 150 mg BID, 200 mg BID, 100 mg QD, 150 mg QD, and 250 mg QD. In the dose escalation phase of the study, there were three dose limiting toxicities (DLTs): two events of Grade 3 lipase elevation in the 100 mg BID and 200 mg BID cohorts (one in each cohort) and one event of Grade 4 CPK elevation in the 150 mg QD cohort. Both the lipase and CPK elevations, although DLTs per protocol, were considered clinically insignificant by the Investigator and Sponsor due to the events being asymptomatic.

The RP2D was determined to be 150 mg QD, and different expansion cohorts have been opened.

The following sections present clinical data for the 70 patients that have been enrolled as of 28 July 2017.

1.3.2.1. Clinical Safety

DCC-2618 has been well tolerated with no clear safety signal observed to-date. Table 4 summarizes the most frequently reported treatment-emergent adverse events (TEAEs) in >10% of patients in Clinical Study DCC-2618-01-001.

Table 4: Summary of TEAEs Occurring in >10% of Patients (All Grades)

		<100 mg/d (N = 8)		≥ 100 mg/d (N = 62)[5]	
Event Term	**Total Events**	**G1/2**	**G3/4**	**G1/2**	**G3/4**
Lipase increased	33	5	1	15	12[3]
Fatigue	32	6	0	25	1
Anaemia	29	1	1	9	18
Decreased appetite[1]	20	1	0	17	1
Diarrhoea	16	1	0	15	0
Alopecia	15	1	0	14	0
Hypertension	15	0	1	9	5
Amylase increased	14	3	0	10	1
Myalgia	14	2	0	12	0
Weight decreased	14	1	0	13	0
Dyspnoea[2]	13	4	0	8	1
Abdominal pain	11	3	0	7	1
Constipation	11	4	0	7	0

		<100 mg/d (N = 8)		≥ 100 mg/d (N = 62)[5]	
Event Term	**Total Events**	**G1/2**	**G3/4**	**G1/2**	**G3/4**
Nausea	11	2	0	9	0
Palmar-plantar erythrodysaesthesia syndrome	11	0	0	11	0
Arthralgia	10	2	0	8	0
Blood bilirubin increased[4]	10	1	0	7	2
Rash	8	2	0	6	0

[1]01-005 has a "Decreased appetite" AE with no severity grade. This is included in the total events column but nowhere else; [2]03-010 has a "Dyspnoea" AE that resulted in death (severity G5). This is included in the G3/4 column for the ≥ 100 mg/d group; [3]Two events of G3 lipase elevation at 100 mg & 200 mg BID were considered DLTs per protocol, although they were not deemed clinically significant by the Investigator and Sponsor; [4]Unconjugated bilirubin, both patients are homozygous for 28 *(TA)7/(TA)7 UGT1A1 polymorphism; 21 of the 62 patients were treated with RP2D of 150 mg QD.

Skin abnormalities, including confirmed SCCs (N=3) have been observed. Events of SCC, keratoacanthoma, and actinic keratosis are considered adverse events of special interest (AESIs).

1.3.2.2. Clinical Pharmacokinetics and Pharmacodynamic Markers

Nonclinical studies had identified DP-5439 as an active metabolite of DCC-2618 with similar activity profile to its parent compound.

The long plasma $T_{1/2}$ of the metabolite (30-60 hours) suggests that QD dosing is feasible. The food effect sub-study has shown that taking DCC-2618 with food should not have a negative impact on absorption. See Section 1.4.2 for further details on the dose, regimen, and treatment duration rationale for the present study.

DCC-2618 leads to rapid clearance of a broad spectrum of KIT mutations from plasma cfDNA in patients with heavily pretreated GIST. Overall, a high total plasma concentration, determined as $C_{max,}$ was observed exceeding 5 µM (3,000 ng/mL) starting at 100 mg BID at Cycle 1 Day 15; the observed mean exposure exceeds targeted plasma levels by far, including exposures required for inhibition of the KIT mutations least sensitive to DCC-2618 (V654A and T670I).

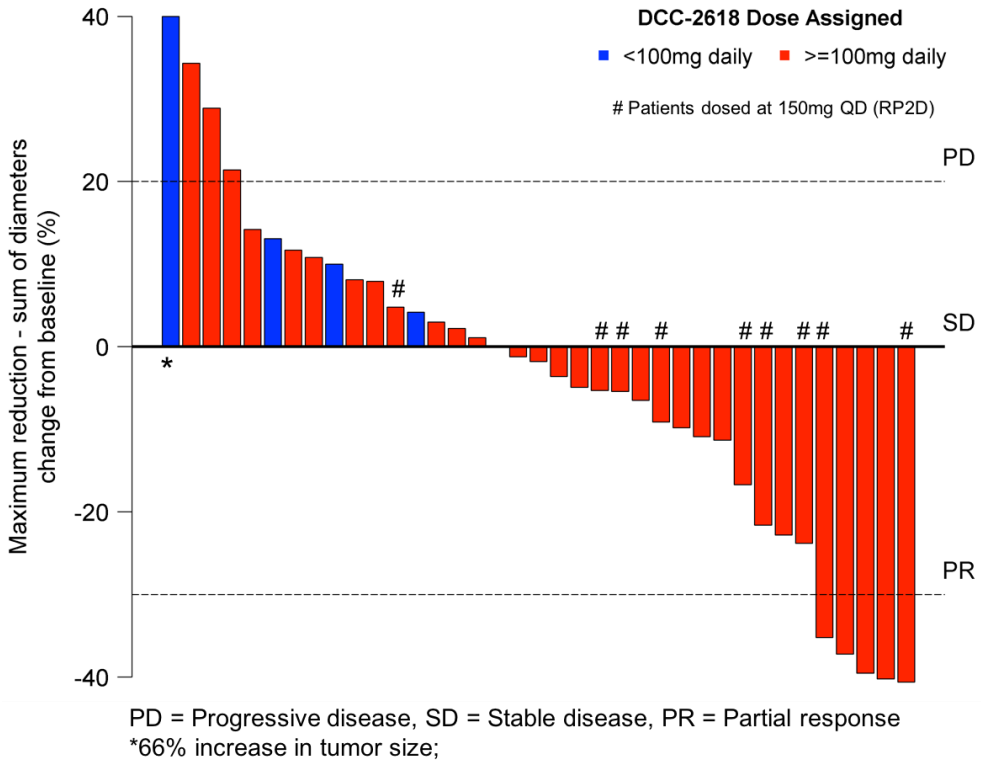
Next-generation sequencing of plasma cell-free DNA (cfDNA) was performed in all GIST patients at baseline and every 2 cycles while a patient is on study. Mutations were detected and quantitated by Guardant 360 v2.9 or v2.10. Only amino acid-altering mutations in KIT and PDGFRA were considered resistance mutations. Cell-free DNA was not detected in all patients. Based on the preliminary data, 19 mutations in unique genes were observed in 11/29 patients with KIT-mutant GIST. Across exons 9, 11, 13, 14, 17, and 18, a total of 43 mutations were detected in the KIT gene. The PDGFRA D842V-mutation was detected in only 1 cfDNA patient sample out of 4 PDGFRA D842V-mutant patients enrolled (confirmed by archival testing).

1.3.2.3. Clinical Efficacy

Efficacy data (measured by Response Evaluation Criteria in Solid Tumors [RECIST] Version 1.1) are available for 37 patients with KIT- or PDGFRA-known mutant GIST. The waterfall plot (Figure 3) is representative of the 37 GIST patients. Data are based on local review of CT scans. Data show patients who were treated at doses <100 mg daily and doses

≥100 mg daily. Patients who received the RP2D of 150 mg QD are noted an '#' in the figure. In the ≥100 mg daily dose cohorts there were 5 partial responses (PR), 25 stable disease (SD), and 3 progressive disease (PD). In the <100 mg dose cohorts there were 3 SD, 1 PD and zero PR.

Figure 3: Best Radiographic Response per RECIST in KIT and PDGFRA GIST Patients (N=37)



^{18}F-Fluorodeoxyglucose positron emission tomography (FDG-PET) scans were performed in GIST patients as an early marker of tumor activity and treatment response to DCC-2618. Scans were obtained at baseline and during Cycle 1 approximately 21 days after the start of continuous dosing. Response was assessed according to European Organization for Research and Treatment of Cancer (EORTC) PET response criteria by a central imaging review. As of Amendment 3, the Sponsor no longer requires FDG-PET scans to be performed in the Escalation Phase because sufficient data supporting an impression of strong antitumor metabolic activity in KIT-mutant GIST patients are available. In the Expansion Phase, FDG-PET scans will be performed for GIST patients that progress and dose escalate (ie, intra-patient dose escalation).

Across the dose levels examined to date, no clear evidence for increased activity at higher dose levels was observed based on PD markers. Partial metabolic responses (PMRs) determined by FDG uptake in PET scans were observed as early as 30 mg BID in 1 GIST patient treated at that dose level and a baseline PET scan.

1.4. Rationale

1.4.1. Study Rationale

Once patients have received imatinib, sunitinib, and regorafenib, there are no other approved treatment options for patients with advanced or unresectable GIST. For patients who have progressed on the approved agents, progression of KIT-driven tumors is primarily based on development of further KIT resistance mutations that are highly heterogeneous. In studying patients who have failed prior approved treatment options and whom may have acquired multiple resistance mutations, the ability to conduct a study with an acceptable active comparator is difficult. There are limited data to support that rechallenge with prior failed treatment options may offer minor benefit. A Korean, single-center, randomized, placebo-controlled study (ie, 'RIGHT Trial') demonstrated that a rechallenge with imatinib provides a small benefit (median PFS of 1.8 months) to some patients compared to placebo (median PFS of 0.9 months) (26). Nevertheless, the study did not show any accompanied symptom palliation based on a health-related quality of life sub analysis using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-item (EORTC QLQ-C30) (27). The RIGHT Trial generally excluded patients who had a limited benefit from initial treatment with imatinib (defined as a PFS of ≤6 months), and thus the patient population was skewed towards ensuring enrollment of patients who had greater initial success on imatinib. A rechallenge with imatinib is not an approved treatment option anywhere in the world, and some treating physicians would rather choose sunitinib depending on the patient history.

DCC-2618 was developed as a pan-KIT and PDGFRA inhibitor. Patients with GIST in the Phase 1 first-in-human study, DCC-2618-01-001, are heavily pre-treated and considered to be tyrosine kinase inhibitor (TKI) resistant. DCC-2618 shows compelling activity in this mutationally diverse KIT patient population based on a high incidence of PMRs, 3 PRs, and 20 patients with SD per RECIST Version 1.1. Initial plasma cfDNA data obtained in the Phase 1 study are in line with nonclinical data demonstrating activity against all KIT and PDGFRA mutations tested. The Guardant 360 panel was used to detect and monitor mutation allele frequency in cfDNA. In patients with heavily pre-treated TKI-resistant GIST, DCC-2618 has led to notable decreases in mutation allele frequency (MAF) of resistance mutations in KIT exons 13, 14, 17 and 18 as well as PDGFRA D842V. The observed clinical activity and the reduction of MAF supports DCC-2618 activity in patients who failed up to 7 prior anticancer treatments.

A double-blinded Phase 3 placebo-controlled study provides the best option to adequately assess the benefit of DCC-2618 in this difficult to treat, highly heterogeneous patient population. Study DCC-2618-03-001 is a Phase 3, interventional, double-blind, placebo-controlled study to assess the safety and efficacy of DCC-2618 in patients with advanced GIST who have received treatment with prior anticancer therapies. Patients will be randomized to the active arm, DCC-2618 + best supportive care (hereafter referred to as "DCC-2618"), or and the control arm, placebo + best supportive care (hereafter referred to as "placebo").

To address the ethical concern of patients with advanced cancer receiving placebo, the study will allow for crossover of patients on the placebo arm who radiographically progress per modified RECIST by independent radiologic review. Tumor assessments are scheduled initially after each cycle to allow for an early detection of disease progression.

Additionally, the study will include a 2:1 randomization scheme to the study, which will also minimize the number of patients that receive placebo. The study will randomize approximately 120 patients, randomized 2:1 (DCC-2618:placebo). This sample size was

selected based on considerations for PFS, objective response rate (ORR), and rate to detect rare safety events and overall exposure to DCC-2618, recommended by FDA.

1.4.2. Dose, Regimen, and Treatment Duration Rationale

1.4.2.1. Nonclinical Pharmacology and Clinical Pharmacokinetic Analyses to Support Optimal Phase 3 Dose Selection

This section addresses the scientific justification for the selection of a 150 mg QD dose regimen for the Phase 3 study of DCC-2618 in patients with advanced GIST. The dose recommendation is based on nonclinical pharmacology, clinical PK assessment, and PD results of the ongoing Phase 1 study (up to 01 June 2017). Upon completion of the Phase 1 study, clinical PK analysis and evaluation of the exposure-response relationship shall be updated.

1.4.2.1.1. In Vitro Pharmacology

The in vitro pharmacology studies demonstrated DCC-2618 and its active metabolite DP-5439 potently inhibit the wild-type and oncogenic KIT variants with IC_{50} values in the range of 3-20 nM (Table 5). Data for the currently available KIT inhibitors, imatinib, sunitinib, and regorafenib, are shown for reference. Imatinib, sunitinib, regorafenib and DCC-2618 all have active metabolites. The following dose considerations are primarily based on the pharmacological properties of the parent compounds.

Table 5: In vitro Inhibition of Recombinant KIT and KIT Mutants

	wt KIT	KIT V654A exon 13	KIT T670I exon 14	KIT D816H exon 17	KIT D816V exon 17	KIT ΔV559-V560/D816V exons 11&17
	IC_{50} (nM)					
Imatinib	34	606	3,500	>10,000	>10,000	>10,000
Sunitinib	6	3	9	1,800	2,200	770
Regorafenib	3	28	7	120	>3,300	>3,300
DCC-2618	3	11	8	3	8	9
DP-5439	6	15	19	20	11	n.d.

IC_{50}=half maximal inhibitory concentration; n.d.=not determined; wt=wild type

The reported fraction unbound (fu) of imatinib and sunitinib are the same (5%), while in vitro potency of sunitinib is approximately 6-fold higher (wt KIT). Correspondingly the daily dosage of sunitinib for GIST (125 µmol, 50 mg) is 6.5-fold lower (based on molar dose ratio) than imatinib (810 µmol, 400 mg). At 0.5% the reported fu of regorafenib is 10-fold lower than sunitinib, while the in vitro potency is 2-fold higher. However, the daily dose of regorafenib (331 µmol, 160 mg) is only 2.6-fold greater (based on molar dose ratio) than sunitinib for GIST, likely due to the inhibition of more KIT mutants.

The measured in vitro fu of DCC-2618 was 0.2% for albumin and 0.6-1.4% for α-1 acid glycoprotein, closer to that of regorafenib (fu=0.5%) than imatinib or sunitinib (fu=5%). The molecular weight of DCC-2618 (510.4 Dalton) is slightly greater than that of regorafenib (482.8 Dalton). As such the projected daily dose of DCC-2618 for GIST (294 µmol, 150 mg) is similar to regorafenib (331 µmol, 160 mg), although the optimal dose could be lower given more potent inhibition of KIT mutants exon 17 and 11 by DCC-2618.

1.4.2.1.2. In vivo Pharmacology

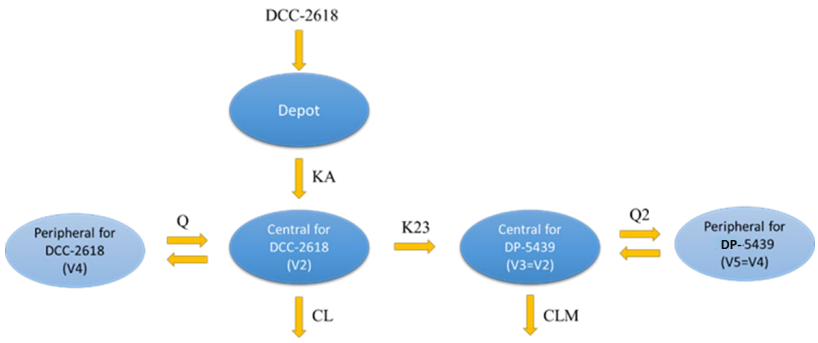
In an exon 11 mutant KIT GIST T1 cell line xenograft mouse model, KIT signaling was suppressed by 69-88% out to 8 hours after administration of a single oral dose of 50 mg/kg DCC-2618 and sustained at ~40% inhibition at 12 hours post dose. After oral, BID dosing in the GIST T1 xenograft model, DCC-2618 significantly inhibited tumor growth, with 90% suppression at 50 mg/kg. In an imatinib-resistant GIST patient-derived xenograft model, 100 mg/kg QD or 50 mg/kg BID DCC-2618 completely stopped the tumor growth. In the Kasumi-1 AML xenograft model expressing a primary exon 17 KIT mutation (N822K KIT), both 100 mg/kg and 50 mg/kg doses of DCC-2618 exhibited robust efficacy while imatinib was ineffective at a dose of 50 mg/kg BID.

From in vivo pharmacology studies, the target PK exposure for tumor growth inhibition was determined to be 10,000 ng·h/mL for $AUC_{0\text{-}24hr}$ of DCC-2618 and DP-5439 at steady-state.

1.4.2.1.3. Clinical Pharmacokinetics Assessment

A population PK analysis was performed on pooled BID and QD data collected from the ongoing Phase 1 study of DCC-2618 in patients with advanced malignancies (Protocol DCC-2618-01-001). The model structure is shown in Figure 4. The PK profiles of DCC-2618 and DP-5439 are both described by two-compartment models. Depot represents the GI tract for orally administered DCC-2618. KA is the first-order absorption rate constant of DCC-2618 and K23 is the first-order rate constant for the metabolism of DCC-2618 to its active metabolite DP-5439 by CYP3A4/5. CL and CLM represent the clearance of DCC-2618 by other enzymatic pathways and the clearance of DP-5439, respectively. To avoid overparameterization, the central and peripheral distribution volumes of DP-5439 were assumed to be the same as those of DCC-2618.

Figure 4: Pharmacokinetic Model of DCC-2618 and DP-5439 in Patients with Advanced Malignancies



Despite the small number of patients in each cohort, population analysis of pooled data across BID and QD cohorts (n=44 total) indicated dose-proportional PK for both DCC-2618 and DP-5439 in cancer patients. The model-predicted steady-state PK exposure as shown in Table 6.

Table 6: Model-predicted Typical Steady-State Pharmacokinetic Exposure of DCC-2618 and DP-5439 in Patients with Advanced Malignancies

Dosing Interval	Dose	Analyte	C_{trough} (ng/mL)	C_{max} (ng/mL)	AUC_{0-24hr} (ng·h/mL)
BID	20	DCC-2618	131	171	3736
		DP-5439	207	225	5211
		Combined	338	396	8947
	30	DCC-2618	197	257	5603
		DP-5439	310	337	7816
		Combined	507	594	13419
	50	DCC-2618	328	428	9339
		DP-5439	517	561	13027
		Combined	845	989	22366
	100	DCC-2618	655	857	18678
		DP-5439	1034	1123	26054
		Combined	1689	1980	44732
	150	DCC-2618	983	1285	28017
		DP-5439	1551	1684	39081
		Combined	2534	2969	67098
	200	DCC-2618	1311	1714	37356
		DP-5439	2068	2246	52108
		Combined	3379	3960	89464
QD	100	DCC-2618	249	510	9348
		DP-5439	457	609	13041
		Combined	706	1119	22389
	150	DCC-2618	373	766	14021
		DP-5439	685	914	19562
		Combined	1058	1680	33583

C_{trough}=concentration at the end of a dosing interval; C_{max}=maximum concentration; AUC_{0-24hr}=area under the concentration × time curve from 0 to 24 hours; BID=twice daily; QD=once daily

The population PK analysis indicated that at DCC-2618 dose regimens of 30-200 mg BID or 100-150 mg QD in a typical cancer patient, the combined steady-state PK exposure (AUC_{0-24hr}) of DCC-2618 and DP-5439 exceeds the 10,000 ng·h/mL threshold for efficacy identified from xenograft mouse studies. However, the observed PK of both DCC-2618 and DP-5439 were highly variable among patients.

Using the population PK model, a simulation was conducted based on 100 clinical studies, each including 100 patients, in order to estimate the proportion of patients achieving the 10,000 ng·h/mL threshold for efficacy. Results showed that a dose of 150 mg QD (estimated from comparative in vitro pharmacology) is predicted to maintain the PK exposure above 10,000 ng·h/mL in 93.6% of patients. The simulation was repeated with a dose of 100 mg QD, at which 87.9% of patients are predicted to reach the efficacy threshold.

1.4.2.1.4. Summary

An oral QD dose of 150 mg DCC-2618 is recommended as the optimal dose regimen for the treatment of GIST based on the following considerations:

- Comparison of in vitro pharmacological properties of DCC-2618 and 3 approved targeted therapies for GIST suggests an efficacious daily dose of ≤160 mg for DCC-2618 in patients with GIST
- In vivo pharmacology studies in xenograft mouse models indicated a target combined PK exposure (AUC_{0-24hr} =10,000 ng·h/mL) of DCC-2618 and DP-5439 for tumor growth

inhibition. A daily oral dose of 150 mg is predicted to maintain the PK above this threshold in 93.6% of patients.

- Both in vitro and in vivo pharmacology data are consistent in predicting that 150 mg QD will be an efficacious dose.
- Safety data collected from the Phase 1 study support administration of 150 mg QD as a tolerable dose.

Further points of consideration are listed below:

- Comparing with BID regimens that are predicted to achieve the exposure target for efficacy, daily dosing is more convenient and may improve treatment adherence. Therefore, the 150 mg QD regimen is preferred over a similar daily dose given BID.
- Due to the large PK interindividual variability, doses lower than 150 mg will result in PK exposure falling below the efficacy threshold in more patients. On the other hand, further improvement in efficacy is likely incremental at a higher dose.
- A dose of 100 mg QD is predicted to reach the exposure target for efficacy in a large majority (87.9%) of patients. If individual patients experience lack of tolerance at 150 mg QD, the dose could be lowered to 100 mg QD potentially without compromising efficacy.
- Further PK-efficacy and PK-safety assessments are being conducted to confirm the selection of 150 mg QD as the optimal regimen for DCC-2618 in patients with GIST.

1.4.2.2. Intra-patient Dose Escalation After Disease Progression

Dose escalation of other TKIs (imatinib) is already a therapeutic option for patients with primary, as well as secondary resistance to standard doses of imatinib.

Based on the population PK model simulations, by using the 150 mg QD regimen, around 93% of patients are predicted to achieve the exposure target for efficacy. Due to the large PK inter-individual variability, doses lower than 150 mg will result in PK exposure falling below the efficacy threshold in more patients. On the other hand, further improvement in efficacy is likely incremental at a higher dose.

The Sponsor acknowledges the challenges of dosing optimization and regards well monitored dose escalation at the time of disease progression as an innovative approach to avoid the selection of an effective but intolerable dose.

Dose escalation at the time of disease progression allows for an exploratory exposure-outcome comparison in individual patients originally assigned to an active dose level and should provide important information for an integrated safety and efficacy analysis.

2. STUDY OBJECTIVES

2.1. Primary Objective

- To assess the efficacy (PFS) of DCC-2618 by independent radiologic review in patients with advanced GIST who have received prior anticancer therapies

2.2. Secondary Objectives

2.2.1. Key Secondary Objectives

- To assess objective response rate (ORR) by independent radiologic review

2.2.2. Secondary Objectives

- To assess other parameters of efficacy, including but not limited to time to progression (TTP) and overall survival (OS)
- To assess the pharmacokinetics/pharmacodynamics (PK/PD) relationship of DCC-2618
- To assess the robustness of efficacy using a sensitivity analysis
- To assess improvement of disease-related symptoms and quality of life
- To assess the safety of DCC-2618

2.3. Exploratory Objectives

- To assess the efficacy of DCC-2618 in patients after dose escalation to DCC-2618 150 mg BID
- To characterize KIT and PDGFRA gene resistance mutations (and potentially other gene mutations) and their DCC-2618-driven longitudinal mutation allele frequency changes in plasma cfDNA
- To retrospectively correlate KIT and PDGFRA mutation/s and/or their frequency (as well as of potentially other gene mutations) in baseline cfDNA with clinical benefit
- To understand potential TKI-resistance mechanisms of GIST at time of progression
- To determine concordance between KIT, PDGFRA, and other mutations in tumor and cfDNA at baseline
- To assess healthcare utilization in patients with advanced GIST who have received approved therapies

3. STUDY DESIGN

3.1. Overview of Study Design

This is a 2-arm, randomized, placebo-controlled, double-blind, international, multicenter study comparing the efficacy of DCC-2618 to placebo in patients who have received treatment with prior anticancer therapies. Prior anticancer therapies must include treatment with imatinib, sunitinib, and regorafenib (3 prior therapies). Up to 40% of enrolled patients may have received prior treatment with imatinib, sunitinib, regorafenib, and other drugs (≥4 prior therapies). Approximately 120 patients will be randomized in a 2:1 ratio to DCC-2618 150 mg QD or placebo (see Figure 1). Randomization will be stratified by:

- Patients who have received 3 prior anticancer treatments versus patients who have received ≥4 prior anticancer treatments
    - It should be noted that enrollment for patients who have received ≥4 prior anticancer treatments will be limited to 40% of the overall sample size.
- Eastern Cooperative Oncology Group (ECOG) performance status (PS)=0 versus ECOG PS=1 or 2

The primary response for the study will be evaluated using the modified RECIST Version 1.1 - GIST-specific (hereafter referred to as "modified RECIST") based on independent radiologic review.

Upon disease progression by modified RECIST based on independent radiologic review, study drug treatment will be unblinded. At that time:

- **Patients randomized to DCC-2618 150 mg QD** will be given the option to:
    - continue DCC-2618 at an increased dose of 150 mg BID (See Section 5.2.1 for more details on intra-patient dose escalation), or
    - continue treatment on study with the same dose if the Investigator feels the patient is receiving benefit from DCC-2618 or if dose escalation may not be tolerable for the patient (dose escalation is not permitted at a later time during the study), or
    - discontinue DCC-2618.
- **Patients randomized to placebo** will be given the option to:
    - cross over to receive DCC-2618 150 mg QD, or
    - discontinue the study.

Patients randomized to placebo who cross over to receive DCC-2618 150 mg QD and have disease progression by modified RECIST based on Investigator assessment will be given the option to:

- continue DCC-2618 at an increased dose of 150 mg BID (See Section 5.2.1 for more details on intra-patient dose escalation),
- continue treatment on study with the same DCC-2618 dose if the Investigator feels the patient is receiving benefit from DCC-2618 or if dose escalation may not be tolerable for the patient (dose escalation is not permitted at a later time during the study), or,
- discontinue DCC-2618.

3.2. Number of Patients

Approximately 120 patients (approximately 80 randomized to DCC-2618 and approximately 40 randomized to placebo) will be enrolled in this study at approximately 35 centers globally.

3.3. Duration of Study

Patients will be treated on their assigned arm until they develop progressive disease, experience unacceptable toxicity, or withdraw consent. At the time of progressive disease by modified RECIST based on independent radiologic review and following unblinding of study drug treatment, patients receiving DCC-2618 will be allowed to dose escalate, continue on the same dose, or discontinue DCC-2618; and patients receiving placebo will be allowed to cross over to receive DCC-2618 and can dose escalate, continue on the same dose, or discontinue DCC-2618 upon further progression by Investigator assessment.

Patients will be eligible to receive study drug for up to 2 years or until commercial supply of the drug is available. This will be extended by agreement between the Sponsor and Investigator for patients who exhibit evidence of clinical benefit and tolerability to the drug, and who adhere to the study procedures. The study will end following the last patient last visit.

4. STUDY POPULATION

4.1. Inclusion Criteria

Patients must meet all of the following criteria to be eligible to enroll in the study:

1. Male or female patients ≥18 years of age at the time of informed consent
2. Histologic diagnosis of GIST
3. Patients must have progressed on imatinib, sunitinib, and regorafenib or have documented intolerance to any of these treatments despite dose modifications.
4. ECOG PS of 0 to 2 at screening.
5. Able to provide an archival tumor tissue sample if no anticancer therapy was administered since the sample was collected; otherwise, a fresh tumor tissue sample is required prior to the first dose of study drug.
6. Female patients of childbearing potential must have a negative serum beta-human chorionic gonadotrophin (β-hCG) pregnancy test at screening and a negative pregnancy test at Cycle 1 Day 1 prior to the first dose of study drug.
7. Patients of reproductive potential must agree to follow the contraception requirements outlined in Section 6.11.10.
8. The patient is capable of understanding and complying with the protocol and has signed the informed consent document. A signed informed consent form must be obtained before any study-specific procedures are performed.
9. At least 1 measurable lesion according to modified RECIST Version 1.1 (non-nodal lesions must be ≥1.0 cm in the long axis or ≥ double the slide thickness in the long axis) within 21 days prior to the first dose of study drug.
10. Adequate organ function and bone marrow reserve as indicated by the following laboratory assessments performed at screening.

- ANC ≥1000/µL
- Hemoglobin ≥8 g/dL
- Platelet count ≥75,000/µL
- Total bilirubin ≤1.5 x the upper limit of normal (ULN)
- Aspartate transaminase and alanine transaminase ≤3 x ULN (≤5x ULN in the presence of hepatic metastases)
- Serum creatinine ≤1.5 x ULN or creatinine clearance ≥50 mL/min based on either urine collection or Cockcroft Gault estimation
- Prothrombin time (PT), international normalized ratio (INR), and partial thromboplastin time ≤1.5 x ULN. Patients on a stable, maintenance regimen of anticoagulant therapy for at least 30 days prior to study drug administration may have PT/INR measurements >1.5 x ULN if, in the opinion of the Investigator, the patient is suitable for the study. An adequate rationale must be provided to the Sponsor prior to randomization.

11. Resolution of all toxicities from prior therapy to ≤Grade 1 (or baseline) within 1 week prior to the first dose of study drug (excluding alopecia and ≤Grade 3 clinically asymptomatic lipase, amylase, and creatine phosphokinase laboratory abnormalities).

4.2. Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study:

1. Treatment with anticancer therapy, including investigational therapy, or investigational procedures within 14 days or 5 x the half-life (whichever is longer) prior to the first dose of study drug. For prior biological therapies, eg, monoclonal antibodies with a half-life longer than 3 days, the interval must be at least 28 days prior to the first dose of study drug.
2. Prior treatment with DCC-2618
3. Prior or concurrent malignancy whose natural history or treatment have the potential to interfere with the safety or efficacy assessment of DCC-2618. Patients receiving adjuvant cancer treatment are not eligible if those medications are potentially active against GIST or excluded per protocol (refer to Section 5.12.3).
4. Patient has known active central nervous system metastases.
5. New York Heart Association class II - IV heart disease, active ischemia or any other uncontrolled cardiac condition such as angina pectoris, clinically significant cardiac arrhythmia requiring therapy, uncontrolled hypertension, or congestive heart failure.
6. Arterial thrombotic or embolic events such as cerebrovascular accident (including ischemic attacks) or hemoptysis within 6 months before the first dose of study drug.
7. Venous thrombotic events (eg, deep vein thrombosis) or pulmonary arterial events (eg, pulmonary embolism) within 3 months before the first dose of study drug. Patients with venous thrombotic events ≥3 months before the first dose of study drug on stable anticoagulation therapy are eligible.
8. 12-lead ECG demonstrating QT interval corrected by Fridericia's formula (QTcF) >450 ms in males or >470 ms in females at screening or history of long QT interval corrected (QTc) syndrome.
9. Left ventricular ejection fraction (LVEF) <50% at screening.
10. Use of proton-pump inhibitors within 4 days prior to the first dose of study drug. Other medications that increase gastric pH, ie, histamine H2 receptor antagonists and antacids may be taken provided they are not administered within 2 hours before or after administration of study drug.
11. Use of strong or moderate inhibitors and inducers of CYP3A4, including certain herbal medications (eg, St. John's Wort) and consumption of grapefruit or grapefruit juice within 14 days or 5 x the half-life (whichever is longer) prior to the first dose of study drug. Please refer to the Indiana University Department of Medicine website (http://medicine.iupui.edu/clinpharm/ddis/main-table/) for guidance on medications that inhibit CYP3A4 enzymes.
12. Use of known substrates or inhibitors of BCRP transporters within 14 days or 5 x the half-life (whichever is longer) prior to the first dose of study drug. Please refer to the FDA's website (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm) for inhibitors and substrates.

13. Major surgeries (eg, abdominal laparotomy) within 4 weeks of the first dose of study drug. Following major surgeries >4 weeks prior to the first dose of study drug, all surgical wounds must be healed and free of infection or dehiscence.
14. Any other clinically significant comorbidities, such as uncontrolled pulmonary disease, active infection, or any other condition, which in the judgment of the Investigator, could compromise compliance with the protocol, interfere with interpretation of the study results, or predispose the patient to safety risks.
15. Known human immunodeficiency virus or hepatitis C infection only if the patient is taking medications that are **excluded** per protocol (refer to Section 5.12.3), active hepatitis B, or active hepatitis C infection.
16. If female, the patient is pregnant or lactating.
17. Known allergy or hypersensitivity to any component of the investigational drug product. Patients with a history of Stevens-Johnson syndrome on a prior TKI are excluded.
18. Gastrointestinal abnormalities including but not limited to:
    - inability to take oral medication
    - malabsorption syndromes
    - requirement for IV alimentation.
19. Any active bleeding excluding hemorrhoidal or gum bleeding.

5. STUDY DRUG ADMINISTRATION AND MANAGEMENT

Study drug refers to DCC-2618 and matching placebo.

5.1. Study Drug Description

DCC-2618 will be supplied as 50 mg strength tablets for oral administration. The tablets contain the active pharmaceutical ingredient formulated as a [redacted] % w/w [redacted] on a hydroxypropyl methylcellulose acetate succinate, [redacted] %). Other excipients include microcrystalline cellulose [redacted] %), lactose [redacted] %), cross-linked polyvinylpyrrolidone [redacted] %), fumed silica [redacted] %), and magnesium stearate [redacted] %).

Placebo will be supplied as identically sized and color-matched tablets.

5.2. Study Drug Dose and Administration

Study drug may be dispensed only under the supervision of the Investigator or an authorized designee and only for administration to study patients. Patients will be randomized to receive 150 mg QD of DCC-2618 or placebo in repeated 28-day cycles.

The Investigator or designee must instruct the patient to take the study drug as per protocol.

- Patients should be instructed to take their assigned dose at the same time each day.
- Patients should take their study drug dose with a 6-ounce glass of water with or without food.
- Patients must be instructed to swallow the tablets whole. Tablets must not be crushed, chewed, or dissolved in liquid or food.
- The date, amount taken, and time of study drug administration must be recorded for the 3 days prior to PK sample collections and on the days of PK sample collection.
- On days of scheduled visits, the dose of study drug must be administered at the site after pre-dose assessments have been completed. The date, amount taken and time of study drug administration must be recorded.

If a patient dose escalates to 150 mg BID of DCC-2618, the Investigator or designee must instruct the patient to take the study drug as per protocol.

- Patients should be instructed take the study drug twice a day, at least 6 hours apart, and at the same time each day.
- Patients should take their study drug dose with a 6-ounce glass of water with or without food.
- Patients must be instructed to swallow the tablets whole. Tablets must not be crushed, chewed, or dissolved in liquid or food.
- The date, amount taken, and time of study drug administration must be recorded for the 3 days prior to PK sample collections and on the days of PK sample collection.
- On days of scheduled visits, the dose of study drug must be administered at the site after pre-dose assessments have been completed. The date, amount taken and time of study drug administration must be recorded.

If a patient forgets to take a dose at the scheduled time, the patient can take the scheduled dose if taken within 8 hours of the scheduled time that was missed for QD dosing and within 4 hours of the scheduled time that was missed for BID dosing. If more than 8 hours (for QD dosing) or 4 hours (for BID dosing) have passed after the scheduled time, then that missed

dose must be omitted and the patients must continue treatment with the next scheduled dose. On days of planned study visits, patients will be informed to take the study drug at the study site as per the Schedule of Assessments.

If vomiting occurs immediately after taking a dose, that dose must not be "made up," and the patient may be offered prophylactic anti-emetics prior to their next dose.

For information on overdose, refer to Section 7.12.

5.2.1. Intra-patient Dose Escalation

- Patients who are randomized to DCC-2618 150 mg QD and have disease progression by modified RECIST based on independent radiologic review may continue DCC-2618 at an increased dose of 150 mg BID.
- Patients who are randomized to placebo who cross over to receive DCC-2618 150 mg QD and have disease progression by modified RECIST based on Investigator assessment may continue DCC-2618 at an increased dose of 150 mg BID.

Upon disease progression, patients must be counseled on any other available treatment options. At the time of dose escalation, the patient must return to the site for study drug to be dispensed. Detailed instructions will be provided in the Study Reference Manual.

5.2.2. Crossover

Patients randomized to placebo who have disease progression by modified RECIST based on independent radiologic review will be given the option to cross over to receive DCC-2618 150 mg QD. Once the independent radiologic review has confirmed disease progression, the patient's study drug treatment will be unblinded and either the patient may start the crossover procedures, or discontinue if the patient declines to enter the crossover.

The initiation of crossover will start with the assessments described in Cycle 1 Day 1 of Table 2 (Schedule of Assessments for Crossover). Following crossover, if a patient has disease progression by modified RECIST based on Investigator assessment, then the patient may continue DCC-2618 with the same dose if the Investigator feels the patient is receiving benefit from DCC-2618, may dose escalate according to the rules in Section 5.2.1, or may discontinue DCC-2618. Detailed instructions will be provided in the Study Reference Manual.

5.3. Dose Interruption and Modification

Study drug may be interrupted or modified (ie, dose reduction) at the discretion of the Investigator at any time due to adverse event (AE), to accommodate palliative treatment, or for other reasons after consultation with the Sponsor. An interruption must be limited to no more than 1 cycle (28 days). Upon resumption following a dose interruption, the Investigator must continue with the patient's original visit schedule calculated from Cycle 1 Day 1.

5.3.1. Dose Interruption due to Planned Medical Procedures

For surgeries that occur while the patient is on study, the extent of the procedure and rate of healing following the procedure must be taken into consideration. The following guidance applies:

- Planned minimally invasive surgery: study drug must be interrupted for 3 days prior to and 3 days after surgery.

- Planned major surgeries: study drug must be interrupted for a minimum of 5 days prior to surgery and continuation of study drug must be determined after consultation with the Sponsor.
- Unplanned surgery: study drug must be interrupted immediately and continuation of study drug must be determined after consultation with the Sponsor.

5.3.2. Dose Interruption and Modification Due to Toxicity

Study drug may be interrupted or reduced as described in Table 7 at the discretion of the Investigator at any time due to AEs and according to the guidelines described in Table 8, Table 9, and Table 10. Whenever possible, dose reductions must be prospectively discussed with the Sponsor. If study drug is interrupted and then study drug is restarted, the patient should remain on their original cycle schedule.

If any patient requires a dose lower than 50 mg QD or if a patient has had their dose reduced and has disease progression confirmed by the independent radiologic reviewer, the patient must be discontinued from study drug, the End-of-Treatment (EOT) Visit and Safety Follow up Visit must be conducted, and the patient must be followed for overall survival.

Table 7: Dose Reduction Steps for Study Drug

Starting Dose of Study Drug	1ST Dose Reduction	2ND Dose Reduction
150 mg QD	100 mg QD	50 mg QD

Following disease progression by modified RECIST, patients who dose escalate to 150 mg BID and have toxicity must be dose reduced according to the steps outlined in Table 8.

Table 8: Dose Reduction Steps for Patients Who Progressed and Dose Escalated to 150 mg BID

Starting Dose of Study Drug	1ST Dose Reduction	2ND Dose Reduction
150 mg BID	100 mg BID	150 mg QD

If the AE returns to Grade 1 or baseline, the patient may be re-escalated. Efforts must be made to re-escalate the patient to the dose level at which the AE occurred. If the dose level is reduced to the 1st dose reduction level and the AE returns to Grade 1 or baseline, the patient may be re-started at the starting dose level. If a patient has two sequential dose reductions and the AE returns to Grade 1 or baseline at the 2nd dose reduction level, the patient may be re-started at the 1st dose reduction level and must remain at this dose level for 1 cycle without interruption before escalating to the starting dose level.

If the AE leading to dose modification does not return to Grade 1 or baseline within 1 cycle (28 days), then the study drug must be discontinued, unless the event is considered not clinically significant by the Investigator, in which case the possibility of restarting the patient at a reduced dose level may be made after consultation with the Sponsor.

Table 9: Dose Modifications for Dermatologic Toxicities and Arthralgia/Myalgia

Toxicity Grade	Dose Modification Guide
Grade 1	Institute support measures and continue the study drug at the current dose
Grade 2	Institute support measures and continue the study drug at the current dose If no improvement within 7 days, then interrupt the study drug • If the event returns to Grade 1 or baseline within 7 days, resume the study drug at the same dose level • If the event returns to Grade 1 or baseline after 7 days, resume the study drug at a reduced dose level If this is a recurrence, after event returns to Grade 1 or baseline, resume the study drug at a reduced dose level regardless of time to improvement If after a dose reduction the event is maintained at Grade 1 or baseline for at least 1 cycle (28 days) of dosing, consider re-escalating the study drug by 1 dose level
Grade 3	Institute support measures Interrupt study drug for at least 7 days or until the event returns to Grade 1 or baseline (maximum 28 days) • Resume study drug at a reduced dose level If after a dose reduction the event is maintained at Grade 1 or baseline for at least 1 cycle (28 days) of dosing, consider re-escalating the study drug by 1 dose level
Grade 4	Discontinue study drug unless the event is not considered life-threatening. Patients may continue study drug with non-life threatening events upon discussion with the Sponsor.
Any Grade	**Stevens-Johnson Syndrome:** If a patient experiences Stevens-Johnson syndrome (SJS), study drug must be permanently discontinued. The patient should be immediately referred to a hospital for clinical evaluation and supportive care/management per institutional guidelines. Re-administration of study drug is not allowed due to the risk of recurrent SJS. Caution for recurrence of SJS with other similar agents (TKIs for GIST) is advised, as the one patient who has been diagnosed with SJS while being treated with DCC-2618 had a similar reaction while being treated with regorafenib prior to DCC-2618.

Table 10: Dose Modifications and Management of Hypertension

Toxicity Grade	Management Guideline*
Grade 1 **Prehypertension (systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg)**	Continue BP monitoring Continue the study drug at the current dose level
Grade 2 **Systolic BP 140 - 159 mm Hg or** **diastolic BP 90 - 99 mm Hg** **Or** **Symptomatic increase by** **>20 mm Hg (diastolic) or to** **>140/90 mm Hg if previously within normal limits**	Treat BP to achieve diastolic BP ≤90 mmHg and or systolic BP ≤140 mmHg • If BP was previously within normal limits, start antihypertensive monotherapy • If patient is already on antihypertensive medication, titrate dose up Continue the study drug at the current dose level Hold study drug if symptomatic increase by 20 mmHg (diastolic BP) until symptoms resolve and diastolic BP ≤90 mmHg On resuming study drug, continue at the same dose level
Grade 3 **Systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg)** **Or** **More than 1 drug or more intensive therapy than previously indicated**	Treat to achieve diastolic BP ≤90 mmHg and or systolic BP ≤140 mmHg • Start antihypertensive medication and/or • Increase current antihypertensive medication and/or • Add additional antihypertensive medication If symptomatic, hold study drug until diastolic BP ≤90 mmHg and/or systolic BP ≤140 mmHg, and symptoms resolve On resuming study drug, continue at the same dose level If BP is not controlled with addition of a new or more intensive therapy, reduce the study drug by 1 dose level If Grade 3 hypertension recurs despite study drug dose reduction and antihypertensive therapy, reduce the study drug by 1 additional dose level
Grade 4 **Life-threatening consequences (eg, malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis)**	Treat BP per institutional guidelines Discontinue study drug

BP=blood pressure

*If BP remains controlled for at least 1 full cycle (28 days), study drug dose re-escalation is permitted at the Investigator's discretion.

Table 11: Dose Modifications for Treatment Related Adverse Events Other than Dermatologic Toxicities, Arthralgia/Myalgia, and Hypertension

Toxicity Grade	Management Guideline[1]
Any Grade 3 or 4	Interrupt study drug dosing until event has resolved to Grade 1 or baseline Once the AE returns to Grade 1 or baseline, reduce study drug by 1 dose level If a patient tolerates the reduced dose without recurrence of the event for at least one cycle, consider re-escalating the dose of study drug to the prior dose level
Asymptomatic/Not clinically significant Grade 3 or 4 laboratory AEs (including CPK and lipase) that persist ≤10 days	Closely monitor for clinical symptoms and continue the study drug at the current dose level Repeat labs within 10 days.
Asymptomatic/Not clinically significant Grade 3 or 4 laboratory AEs (including CPK and lipase) that persist >10 days	Closely monitor for clinical symptoms; for Grade 4 events, interrupt study drug until the event returns to Grade 3 • Asymptomatic Grade 3 or Grade 4 elevations of plasma enzyme: lipase or CPK do not require dose interruption Once the AE returns to Grade 3, resume the study drug at the current dose level or consider reducing by 1 dose level per Investigator discretion after discussion with the Sponsor.
Clinically Significant Grade 3 or 4 laboratory AEs (including CPK and lipase)	Interrupt study drug. If the Investigator assesses that restarting study drug is in the patient's best interest, the Sponsor must be contacted for discussion and determination if restarting is allowed.

AE=adverse event; CPK=creatine phosphokinase

1. The rules for dose modifications for laboratory AEs will be based on local laboratory results.

5.4. Packaging and Labeling

DCC-2618 will be supplied by the Sponsor as formulated drug in tablets for oral administration containing 50 mg of study drug in 30-count high-density polyethylene (HDPE) bottles with child resistant caps.

Placebo tablets of matching size, shape, and color, will be supplied by the Sponsor in matching 30-count HDPE bottles with child resistant caps.

Study drug labeling will be in accordance with applicable local and national regulations.

Study drug will be provided and replaced via the Interactive Response Technology (IRT). Study drug dispensation instructions will be provided in the Pharmacy Manual.

5.5. Storage Conditions

Study drug bottles must be stored tightly closed between 5°C/41°F and 25°C/77°F, away from sunlight and areas of high humidity (ie, near showers in bathrooms) and according to the instructions provided in the Pharmacy Manual. Excursions between 2°C/35.6°F and 27°C/80.6°F are allowed. While at the clinical site, the study drug must be stored in a secure, temperature-monitored area of limited access and only at the location(s) listed on the Form FDA 1572.

Instructions regarding the storage and handling of study drug after dispensation to patients will be provided to site in the Pharmacy Manual.

5.6. Study Drug Compliance

To ensure study drug compliance, the Investigator or designee must supervise all study drug dosing that occurs at the site. At each visit, site personnel must review that the patient is compliant with study drug dosing and remind the patient of study drug dosing requirements. Compliance must also be assessed by ongoing study drug count.

If a patient demonstrates continued noncompliance of study drug dosing despite educational efforts, the Investigator must contact the Sponsor to discuss discontinuation of the patient from the study.

5.7. Study Drug Accountability

Accountability for the study drug at the study site is the responsibility of the Investigator. The Investigator must ensure that the study drug is used only in accordance with this protocol. Where allowed, the Investigator may choose to assign drug accountability responsibilities to a pharmacist or other appropriate individual. Drug accountability records indicating the study drug's delivery date to the site, study drug inventory at the site, study drug dispensed to each patient, study drug returned by each patient, and study drug returned to the Sponsor or study drug destruction on site must be maintained by the clinical site. Accountability records must include dates, quantities, bottle numbers, and patient numbers. The Sponsor or its designee must review drug accountability at the site on an ongoing basis during monitoring visits. If any dispensing errors or discrepancies are discovered, the Sponsor must be notified immediately.

Patients must be instructed to return all unused, partially used, and used study drug bottles to the site at each visit. The study monitor must verify study drug records and inventory throughout the study.

5.8. Disposal, Return, or Retention of Unused Study Drug

Patients must be instructed to return all used, partially used, and full study drug bottles. The site staff or pharmacy personnel (as appropriate) must retain all materials returned by the patients until returned to Sponsor/designee or destroyed by the study site. If the study drug will be destroyed at the study site, the Investigator or designee, must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by the Sponsor. Destruction must be adequately documented.

5.9. Method of Assigning Patients to Treatment

Patients will be randomized in a 2:1 ratio to DCC-2618 150 mg or placebo. Randomization will be stratified by:

- Patients who have received 3 prior anticancer treatments versus patients who have received ≥4 prior anticancer treatments
    - It should be noted that enrollment for patients who have received ≥4 prior anticancer treatments will be limited to 40% of the overall sample size.
    - Prior anticancer treatments are only counted once and without regard to when the patient received treatment, unless they were given as combination treatments.
- ECOG=0 versus ECOG=1 or 2

The IRT will be used to assign study drug treatment. Detailed instructions for randomization will be provided separately.

5.10. Blinding and Unblinding

This is a double-blind study.

5.10.1. Blinding

The patients and all site personnel, including the Investigator, the site monitor, and the study team must be blinded, with the exception of the following:

- Any site personnel for whom this information is important to ensure the safety of the patient in the event of a life threatening medical emergency
- Any site personnel for whom this information is important to ensure the safety of the patient and their fetus in the event of a pregnancy
- Vendors responsible for pharmacovigilance and regulatory personnel at the Sponsor to satisfy serious adverse event (SAE) processing and reporting regulations
- Clinical Supply Chain
- Unblinded statistician and programmer preparing the final (production) randomization list and unblinded analyses for the independent data monitoring committee (IDMC)
- IDMC
- Vendors analyzing PK and biomarker samples
- Vendor conducting the population PK analysis
- IRT vendor

- The Investigator, patient, site personnel, site monitor and study team will become unblinded to a specific patient's treatment assignment, if the patient has disease progression based on independent radiologic review.

5.11. Unblinding

Instructions for unblinding through IRT will be provided in the Study Reference Manual.

Unblinding of the individual patient's study drug assignment by the Investigator must be limited to the following: medical emergencies in which knowledge of the patient's study drug is necessary for clinical management. In cases of medical emergencies, the Investigator must use their best judgment as to whether to unblind. If the Investigator deems it is not necessary to unblind immediately, the Investigator must first attempt to contact the Sponsor to discuss and agree to the need for unblinding. If the Investigator has tried but is unable to reach the Sponsor, the Investigator must use their best judgment, based on the nature and urgency of the clinical situation, and may proceed with unblinding without having successfully reached and discussed the situation with the Sponsor.

If a patient's study drug assignment has been unblinded for a medical emergency, the Sponsor must be notified within 24 hours of the unblinding event. The reason and the date of the unblinding must be documented clearly in the patient's source documents. Information regarding the study drug assignment obtained from the unblinding must be maintained in a secure location with controlled access and must not be shared with the Sponsor, contract research organization, or any site personnel (other than the physician treating the patient). In addition, the Investigator must consider whether the clinical event that prompted unblinding must be considered an SAE, according to the regulatory definitions or criteria for SAEs, and if so, submit an SAE report, per Section 7.11. If a patient's study drug assignment is unblinded for a medical emergency or urgent clinical situation, the patient must discontinue study drug.

The Sponsor or designee may also unblind any SAE reports in compliance with regulatory reporting requirements. In addition, the Sponsor may, for matters relating to safety concerns, unblind individual patients at any time.

5.12. Prior and Concomitant Treatment and Procedures

5.12.1. Prior Medications and Procedures

Information regarding any medication or non-drug therapy or procedure taken or performed within 30 days prior to screening and before the first dose of study drug must be documented in the patient's source documents and the electronic case report form (eCRF).

5.12.2. Prior Anticancer Medications and Procedures

Any prior anticancer medication or procedure must be documented in the patient's source documents and the eCRF.

5.12.3. Concomitant Medications

All medications, including vitamin supplements, over-the-counter medications, and oral herbal preparations; non-drug therapies taken on or after the first day of study drug dose through and including 30 days after the last dose of study drug must be documented in the patient's source documents and the eCRF. In addition, any new treatments taken after the last dose of study drug through 30 days after the last dose must be documented in the patient's source documents and the eCRF.

The date and time of concomitant H2 receptor antagonist and antacid administration must be recorded 3 days prior to the study visit and on the day of the visit in the patient's source documents and the eCRF.

5.12.3.1. Permitted Medication

Patients may receive medications for symptomatic relief (eg, analgesics, laxatives, antiemetics).

Medications that increase gastric pH (eg, antacids), with the exception of proton pump inhibitors, may be taken provided they are not administered within 2 hours before or after administration of study drug.

5.12.3.2. Medications to Avoid or Take with Caution

The following medications must be avoided or taken with caution following discussion with the Sponsor:

- Strong or moderate inhibitors or inducers of CYP2D6, CYP2C8, or CYP2E1 during treatment with study drug. Please refer to the Indiana University Department of Medicine website (http://medicine.iupui.edu/clinpharm/ddis/main-table/) for guidance on medications that inhibit or induce CYP2D6, CYP2C8, or CYP2E1 enzymes.
- Known substrates or inhibitors of P-glycoprotein 1 (permeability glycoprotein, also known as multidrug resistance protein 1 or MDR1). Please refer to the FDA's website for inhibitors https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table5-2 and substrates https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table5-1 for MDR1.
- Medications that are known substrates of OATP1B1 and OATP1B3. Please refer to the FDA's website (https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table5-1) for known substrates of OATP1B1 and OATP1B3.
- Medications dependent on CYP2C8, CYP2C9, CYP2C19, or CYP2D6 for their metabolism. Please refer to the Indiana University Department of Medicine website (http://medicine.iupui.edu/clinpharm/ddis/main-table/) for guidance on medications. For example:
    - Warfarin may be given but be monitored carefully due to CYP2C9 inhibition by study drug.
    - Plavix (clopidogrel) should be avoided. Plavix is a pro-drug dependent on CYP2C19 for its activity. Co-administration can lead to reduced effects of Plavix.

Patients taking any of the above listed medications must be closely monitored for any potential drug-drug interactions.

5.12.3.3. Prohibited Medications and Substances

Prohibited medications and certain foods are not allowed in this study (from screening through the Safety Follow-up Visit). The following medications must be excluded during the study:

- Proton pump inhibitors must be discontinued at least 4 days prior to the first dose of study drug
- Strong or moderate inhibitors or inducers of CYP3A4, including certain herbal medications (eg, St. John's Wort) must be discontinued at least 14 days or 5 x the half-life (whichever is longer) prior to the first dose of study drug. Please refer to the Indiana University Department of Medicine website (http://medicine.iupui.edu/clinpharm/ddis/main-table/) for guidance on medications that inhibit CYP3A4 enzymes.
- Grapefruit or grapefruit juice at least 14 days prior to the first dose of study drug.
- Known substrates or inhibitors of BCRP transporters must be discontinued at least 14 days or 5 x the half-life (whichever is longer). Please refer to the FDA's website (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm) for inhibitors and substrates for BCRP.
- Anticancer therapies, including investigational therapy, must be discontinued at least 14 days or 5 x the half-life of the drug, whichever is longer, prior to the first dose of study drug. For prior biological therapies, eg, monoclonal antibodies with a half-life longer than 3 days, the interval must be at least 28 days prior to the first dose of study drug.

5.12.4. Concomitant Procedures

All procedures performed on or after the first dose of study drug through and including 30 days after the last dose of study drug must be documented in the patient's source documents and the eCRF.

Surgical resection or palliative radiotherapy during study treatment must be discussed with the Sponsor prior to implementation. If the Investigator and Sponsor agree it is in the best interest of the patient, surgical resection or palliative radiotherapy may be performed; however, the patient must be censored in the PFS analysis from the time surgery or radiotherapy was performed.

5.13. Other Precautions

In order to mitigate the potential risk of photoirritation/phototoxicity, patients must be instructed to avoid strong sunlight, sunlamps, and other sources of ultraviolet radiation for the duration of the study. Prophylactic skin care recommendations for all patients on study drug include sunscreen with SPF ≥30, hypoallergenic moisturizing creams or ointments for dry skin, and gentle skincare with fragrance-free soaps and detergents.

6. STUDY ASSESSMENTS

6.1. Screening

Screening must occur within 28 days prior to the first dose of study drug to confirm that patients meet the selection criteria for the study. Radiologic imaging must be performed within 21 days prior to the first dose of study drug. The assessments to be conducted at screening are provided in Table 1 (schedule of assessments).

6.2. Rescreening

Patients may only be rescreened with the approval of the Sponsor. If a patient is rescreened, all screening assessments must be repeated except tumor tissue sample (as applicable) and ophthalmologic examination. Imaging assessments and dermatologic examination do not need to be repeated if performed within 21 days of the first dose of study drug. Patients may only be rescreened once. If a patient is rescreened, the screening window will begin once the first rescreening assessment has been initiated.

6.3. Treatment Period

Patients will be randomized in the study after confirmation of all eligibility criteria. The first dose of study drug must be administered in the clinic on Cycle 1 Day 1. Study visits during the Treatment Period will occur as shown in Table 1 (schedule of assessments) and Table 2 (schedule of assessments for crossover). Patients will be outpatients during the Treatment Period. All visits must occur within the windows specified.

Patients who prematurely discontinue study drug must return for an EOT Visit within 7 days after the last dose of study drug.

6.4. Follow Up

Patients will be contacted by phone call for the Safety Follow-up Visit within 30 days (+5 days) after the last dose of study drug to assess AEs; medications, including anticancer treatments; and procedures (see Section 6.11.12 for further details). Patients will be contacted by phone call for overall survival (see Section 6.10.2 for further details).

6.5. Lost to Follow Up

A patient will be considered lost to follow up if both of the following occur:

- Patient misses 2 consecutive study visits and is subsequently unable to be contacted by phone call (3 documented attempts by phone within 2 weeks following the second missed visit).
- Patient does not respond within 2 weeks to a registered letter sent after the 3 attempted phone contacts.

6.6. Study Assessments

The study specific assessments are detailed in this section and the schedule of assessments are outlined in Table 1 (schedule of assessments) and Table 2 (schedule of assessments for crossover).

Additional unscheduled safety or efficacy assessments may be performed at any time as clinically indicated to determine the relevance of specific findings and/or the duration of events.

6.6.1. Timing of Assessment

The EORTC QLQ-C30 and EuroQol 5-Dimension 5-Level (EQ-5D-5L) questionnaires must be performed before the patient sees the Investigator or designee on the day of the scheduled visit. If the dermatologic examination or imaging assessments are completed within 7 days of the scheduled visit and the patient does not see the Investigator or designee, the questionnaires do not need to be completed on that day. The EORTC QLQ-C30 must be performed prior to the EQ-5D-5L, followed by the Healthcare Utilization Questionnaire (HCUQ).

All other assessments may be completed in any order as shown in Table 1 (schedule of assessments) and Table 2 (schedule of assessments for crossover).

6.7. Informed Consent Procedure

Each patient must sign and date a study-specific informed consent form (ICF) before any study specific procedures can be performed. The ICF will comply with all applicable regulations governing the protection of patients. An ICF, approved by the Sponsor and the site's Institutional Review Board (IRB)/Independent Ethics Committee (IEC)/Research Ethics Board (REB) must be used. The Investigator or designee must document the consenting process, including the date when the informed consent form was signed in the patient's source document.

6.8. Assigning Patient Number

A unique patient identification number (patient number) will be assigned to each patient once informed consent is obtained. Detailed instructions on assigning patient numbers will be provided in the Study Reference Manual. If a patient is rescreened, the patient retains the original patient number.

6.9. Demographics and Medical History

Demographic information must be collected at screening.

Cancer history and prior treatment (including reason for discontinuation), must be obtained during screening. Cancer history will include:

- Known histologic diagnosis of GIST
- Tumor mutational status
- All prior cancer treatment regimens, including:
  - Surgery (including tumor tissue sample[s]): include date(s), site(s), and extent of resection (eg, tumor tissue sample only, R0, R1, or R2)
  - Systemic therapy: include dates of treatment, agents (including dose and dosing regimen), reason for treatment (eg, adjuvant therapy or for metastatic disease), best response, date of disease progression or date and reason for treatment discontinuation other than disease progression.
  - Radiation therapy: include the site(s) treated, total dose(s), date(s) of treatment, and response(s)
  - Other procedures, such as radiofrequency ablation (if applicable)

Medical history, including any significant conditions or diseases that stopped at or prior to informed consent, must be elicited from each patient during screening. Based on the medical

history, the patient must be assessed for any disqualifying medical conditions as specified in the inclusion and exclusion criteria. The medical history shall include a complete review of systems, past medical and surgical histories, and any allergies. Ongoing conditions are considered concurrent medical conditions; if possible, the start date for these comorbidities must be documented.

6.10. Efficacy

6.10.1. Radiologic Imaging

All patients will have radiographic tumor evaluation by computed tomography (CT) scans of the pelvis, abdomen, and chest according to the schedule of study assessments in Table 1 (schedule of assessments) and Table 2 (schedule of assessments for crossover). Radiologic imaging performed as standard of care prior to informed consent may be used as the Screening assessment as long as the imaging was performed within 21 days prior to the first dose of study drug. Radiologic imaging may be performed up to 7 days prior to the corresponding study visit or post dose at the study visit. An initial indication of a PR or CR based on independent radiologic review must be confirmed ≥4 weeks later. Magnetic resonance imaging (MRI) scans of the abdomen/pelvis and CT scan without contrast of the chest may be used for patients who are allergic to radiographic contrast media. Additionally, for patients whose local regulatory authority and/or ethics committee has not approved use of CT scans, MRIs may be used. Throughout the study, the same assessment technique must be used. Ultrasound scanning is not an acceptable substitute for CT scanning.

Copies of all imaging scans must be obtained and sent to an independent imaging vendor designated by the Sponsor as outlined in a separate protocol specific manual. The independent imaging vendor will assess the quality of the images and be responsible for performing an independent radiologic review.

The independent imaging vendor must ensure that the independent radiologic reviewer remains blinded to the local assessment from the Investigator and other unblinding information. This and all other imaging procedures will be documented in a protocol specific review charter agreed upon between the Sponsor and the independent imaging vendor before initiation of any independent radiologic reviews.

The independent radiologic reviewer and Investigator will assess tumor response using modified RECIST (see Section 9.2.1.1). Response as determined by the Investigator will be recorded in the eCRF. Data from the independent radiologic review will be used for the primary endpoint analysis.

Confirmation of No Disease Progression: If the independent radiologic reviewer confirms that there is no disease progression, the patient will continue to receive study drug unless there is a medical need (ie, rapid progression or clinical deterioration) that requires the study drug to be discontinued. If the Investigator determines progression based upon clinical deterioration, a scan must be performed and reviewed by the independent radiologic reviewer to determine if the patient progressed. The basis for determination of progression per clinical deterioration must be documented in the patient's source documents and eCRF.

Confirmation of Disease Progression: Following confirmation of disease progression by modified RECIST based on independent radiologic review, the patient's treatment assignment will be unblinded via the IRT.

- **Patients randomized to DCC-2618 150 mg QD** will be given the option continue at an increased dose of 150 mg BID, to continue treatment on study with the same dose if the

Investigator feels the patient is receiving benefit from DCC-2618, or discontinue DCC-2618. If a patient continues treatment at the same dose, dose escalation is not allowed at a future time. At the time of dose escalation, the patient must come back to the site for study drug to be dispensed.

- **Patients randomized to placebo** will be given the option to cross over to receive DCC-2618 150 mg QD, or discontinue the study. Crossover patients must follow the schedule of assessments in Table 2.

Confirmation of Disease Progression Following Crossover: Following confirmation of disease progression by modified RECIST based on Investigator review, patients will be given the option to dose escalate according to the rules in Section 5.2.1, continue DCC-2618 at the same dose if the Investigator feels the patient is receiving benefit from DCC-2618, or discontinue DCC-2618. If a patient continues treatment at the same dose, dose escalation is not allowed at a future time. At the time of dose escalation, the patient must come back to the site for study drug to be dispensed.

More details on image acquisition guidelines and radiographic assessment will be provided in a separate protocol specific manual.

6.10.2. Overall Survival Follow-Up by Phone Call

All patients will be followed until withdrawal of consent or death from any cause. After the Safety Follow-Up Visit, patients will be contacted every 3 months (±1 month) to collect long-term survival data.

6.10.3. Patient Reported Outcome Measurements

6.10.3.1. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-item (EORTC QLQ-C30)

The EORTC QLQ-C30 is a validated, standardized, patient-completed questionnaire used extensively in international clinical studies and developed to assess health-related quality of life in patients with cancer (28). The time required for completion is approximately 3-5 minutes. Validated translations will be provided for sites in non-English-speaking countries.

The questionnaire is composed of multi-item and single-item scales. These include 5 functional scales (physical functioning, role functioning, emotional functioning, social functioning, cognitive functioning), 9 symptom scales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), and a global health status/quality of life (QOL) scale.

The functioning and symptoms scales ask the patient to rate his or her experience for a particular item during the last week by selecting Likert scale response options of “not at all,” “a little,” “quite a bit,” or “very much.” The 2 items comprising the global health status scale also evaluate the patient’s experience over the past week using numerical rating scales with 1 representing “very poor” and 7 representing “excellent.”

Patients will be asked to complete EORTC-QLQ-C30 in their native language using an electronic patient reported outcome (ePRO) system on provided tablet computers before dosing at the visits indicated in Table 1 (schedule of assessments) and Table 2 (schedule of assessments for crossover).

6.10.3.2. EuroQol 5-Dimension 5-Level (EQ-5D-5L)

The EQ-5D-5L is a validated, standardized, patient-completed questionnaire developed by the EuroQol group and used commonly in clinical studies to provide a measure of patient utility for clinical and economic appraisals (29). The time required for completion is approximately 2-3 minutes. Validated translations of the EQ-5D-5L will be provided for sites in non-English-speaking countries.

The first 5 items of the EQ-5D-5L measure the health dimensions of mobility, ability to conduct self-care, ability to conduct usual activities, pain/discomfort, and anxiety/depression. The patient will select from 5 response levels (no problems, slight problems, moderate problems, severe problems, extreme problems) to rate their level of difficulty on that dimension that day. The EQ-5D-5L represents a revision to the original EQ-5D-3L (with 3 response levels per item) and has been shown to significantly increase reliability and sensitivity (discriminatory power) while maintaining ease of completion.

The sixth item is a EuroQol visual analogue scale (EQ-VAS). The EQ-VAS records the patient's self-rated health on a vertical scale with endpoints labeled "the best health you can imagine" and "the worst health you can imagine." This information can be used as a quantitative measure of health as judged by the individual patient. A patient is asked to "mark an X on the scale to indicate how your health is TODAY" and "write the number you marked on the scale in the box below."

Patients will be asked to complete EQ-5D-5L after the EORTC-QLQ-C30 in their native language using an ePRO system on provided tablet computers before dosing at the visits indicated in Table 1 (schedule of assessments) and Table 2 (schedule of assessments for crossover).

6.11. Safety

The safety profile will be assessed based on physical examinations; ECOG PS; changes from baseline in vital signs, ECGs, LVEF based on echocardiogram/multigated acquisition scan (MUGA), dermatologic examination, and clinical laboratory tests; and the reporting of AEs.

6.11.1. Physical Examinations

A full physical examination will be performed at screening. A full physical examination includes a review of the following systems: head/neck/thyroid, eyes/ears/nose/throat, respiratory, cardiovascular, lymph nodes, abdomen, skin, musculoskeletal, and neurological. Breast, anorectal, and genital examinations will be performed when medically indicated. At all other visits, examinations will be driven by clinical findings and/or patient complaints. After screening, any clinically significant abnormal findings in physical examinations must be reported as AEs.

6.11.2. Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group PS (30) will be assessed according to the schedule of assessments in Table 1 (schedule of assessments) and Table 2 (schedule of assessments for crossover). ECOG may be performed pre or post dose.

6.11.3. Vital Signs, and Weight and Height

Vital sign measurements, height, and weight will be performed according to the schedule of assessments in Table 1 (schedule of assessments) and Table 2 (schedule of assessments for crossover). Vital sign measurements will include sitting blood pressure, pulse, respiratory

rate, and body temperature. These will be assessed following a 5-minute rest (seated or supine position).

6.11.4. Electrocardiograms

Digital, 12-lead ECGs will be performed with central over-reading according to the schedule of assessments in Table 1 (schedule of assessments) and Table 2 (schedule of assessments for crossover). All sites will be provided with an ECG machine and associated materials by the central ECG diagnostic service.

Performance of all ECGs must adhere to the following guidelines:

- All standard digital ECGs must be performed after the patient has been in the supine or semi-recumbent position for at least 15 minutes. The 15-minute rest period will start after the placement of the ECG leads.
- The ECG must be performed before the dose of study drug.

A hard copy of the ECG must be printed and signed by the Investigator at the site.

ECG data will be transmitted to the central ECG diagnostic service and all interval measurements will be reviewed and adjusted using the central ECG core labs methodology by a trained ECG analyst. A cardiologist at the central ECG diagnostic service will then review each ECG to confirm if intervals were calculated correctly and to provide an interpretation. A report containing this information will be provided to the site for review and signature by the Investigator. This report will be filed with the machine ECG report for each visit in the patient's source documents. The values reported by the central ECG diagnostic service will be used for data analysis.

Heart rate and the following ECG intervals will be captured in the database:

- PR interval
- QT, QTcB (Bazett's corrected QT interval [$QTcB = QT/RR^{0.50}$]) and QTcF ($QTcF = QT/RR^{1/3}$) intervals
- QRS duration
- RR interval

The central ECG diagnostic service's standard reference ranges will be used throughout the study.

6.11.5. Echocardiograms/Multigated Acquisition Scans

Echocardiograms or multigated acquisition scans (MUGAs) will be performed according to the schedule of assessments in Table 1 (schedule of assessments) and Table 2 (schedule of assessments for crossover). Echocardiogram or MUGA performed as standard of care prior to informed consent may be used as the Screening assessment as long as the echocardiogram or MUGA was performed within 28 days prior to the first dose of study drug. The same modality (echocardiogram or MUGA) must be used throughout the study. Left ventricular ejection fraction (LVEF) must be documented in the patient's source documents and eCRF.

6.11.6. Dermatologic Examination

All patients will be assessed by a consulting dermatologist for skin lesions, especially for SCC, actinic keratosis, and keratoacanthomas, according to the schedule of assessments in

Table 1 (schedule of assessments) and Table 2 (schedule of assessments for crossover) and as clinically indicated. The examinations must include the entire skin. Dermatologic exam that meets the protocol criteria that was performed as standard of care prior to informed consent may be used as the Screening assessment as long as the exam was performed within 21 days prior to the first dose of study drug. Any new or changing skin lesions noted during the course of treatment must be documented in the patient's source documents and eCRF. In case of suspected SCC or keratoacanthomas, a skin biopsy must be taken for confirmation of diagnosis by a certified pathologist at the clinical site. Samples with confirmed SCC or keratoacanthoma lesions will be sent to a central laboratory for histopathological and/or molecular analysis.

6.11.7. Ophthalmologic Examination

Ophthalmologic examinations will be performed by a licensed ophthalmologist according to the schedule of assessments in Table 1 (schedule of assessments) and Table 2 (schedule of assessments for crossover) and if clinically indicated during treatment with study drug.

Examinations will include examination of anterior structures (including cornea, anterior chamber, iris, and lens) and posterior structures (including optic nerve, macula, retinal vessels, the retinal periphery, and the vitreous); assessment of intraocular pressure in each eye; assessment of visual acuity.

This examination does not have to be repeated if there is documentation of an examination that met protocol criteria within 28 days before the Screening Visit and after the last dose of previous anticancer treatment.

6.11.8. Clinical Laboratory Tests

Blood and urine samples will be collected according to the schedule of assessments in Table 1 (schedule of assessments) and Table 2 (schedule of assessments for crossover) and analyzed at a central laboratory. All blood samples must be collected while patients are in a seated or supine position. Specific instructions for the collection, processing and shipment of samples will be provided in a separate laboratory manual. Laboratory test results that are abnormal and considered clinically significant must be reported as AEs (Section 7.7.1). Screening laboratory results must be available before randomization. All samples must be collected in accordance with acceptable laboratory procedures and graded for toxicity as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03.

Available local laboratory test results will be used for treatment management decisions (eg, dose modifications [Section 5.3.2]) and initial assignment of CTCAE grading. Every effort must be made to discuss any changes to study drug dosing with the Sponsor before implementation, and only if not feasible beforehand, to inform the Sponsor within the same day. Central laboratory results will be used for final assignment of CTCAE grading. In the case of different grades associated with local versus central laboratory results for AEs, the central laboratory results must be used for documenting AEs.

The safety laboratory tests are provided in Table 12.

Table 12: Safety Laboratory Tests

Serum Chemistry	Hematology	Urinalysis[2]
Glucose	Hemoglobin	Urine protein
Blood urea nitrogen	• Mean corpuscular hemoglobin	Urine blood
Creatinine	• Mean corpuscular hemoglobin concentration	Specific gravity
Sodium		Urine ketones
Potassium	• Mean corpuscular volume	Urine glucose
Calcium	Hematocrit	
Magnesium	Platelets	
Phosphorus	Leukocytes	
Total and direct bilirubin	Reticulocytes	
Alkaline phosphatase	Differential (absolute):	
Aspartate aminotransferase	• Eosinophils	
Alanine aminotransferase	• Basophils	
Lactate dehydrogenase	• Neutrophils	
Total protein	• Lymphocytes	
Albumin	• Monocytes	
Creatine Phosphokinase	**Coagulation Studies[1]**	
Globulin	Activated partial thromboplastin time	
Triglycerides	Prothrombin time	
Lipase	International Normalized Ratio	
Amylase		
Thyroid Testing		
Thyroid stimulating hormone (TSH)		
Free triiodothyronine (T3)		
Free thyroxine (T4)		

1. For patients taking anticoagulants, testing will be performed according to Table 1 (schedule of assessments) and Table 2 (schedule of assessments for crossover). Monitoring of coagulation tests must be increased for as long as deemed clinically appropriate following a change in anticoagulant dose during the study.
2. If any result is abnormal, a microscopic analysis must be performed by the central laboratory.

6.11.9. Pregnancy Test

A serum β-hCG test to rule out pregnancy in women of childbearing potential will be obtained at screening and analyzed at a central laboratory. A urine pregnancy test will be completed at all other visits as outlined in Table 1 (schedule of assessments) and Table 2 (schedule of assessments for crossover). A serum pregnancy test may be performed instead of urine if it is the site's standard practice and the results are received prior to the patient being dosed in the clinic. Pregnancy testing will not be required for patients who are non-childbearing females, defined as one who is post-menopausal (amenorrheic for ≥12 months with a follicle stimulation hormone (FSH) ≥40 mIU/mL) or has documented complete oophorectomy or hysterectomy.

6.11.10. Contraception and Pregnancy Avoidance Measures

6.11.10.1. Contraception

The effects of DCC-2618 on sperm, conception, pregnancy, and lactation are not known. Participation in this study requires patients to agree to use 2 methods of contraception with one of the methods being highly effective. Methods of contraception must be in successful use from at least 14 days prior to the first dose of study drug and until 104 days following the last dose of study drug.

Contraception for the patient is waived for the following:

- True abstinence for the patient, when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, and postovulation methods) and withdrawal are not acceptable methods of contraception.
- If the male has documented bilateral orchiectomy or is considered infertile as documented through examination of a semen specimen or by demonstration of the absence of the vas deferens by ultrasound before the first dose of the study drug.
- If the female is of non-childbearing potential, per the following:
  - Postmenopausal: spontaneous amenorrhea for at least 12 consecutive months and have a serum FSH level ≥40 mIU/mL
  - Documented hysterectomy or a bilateral oophorectomy/salpingo-oophorectomy

NOTE: All other female patients (including patients with tubal ligations and patients who do not have a documented hysterectomy) will be considered to be of childbearing potential.

Acceptable highly effective methods of contraception:

- Vasectomy 6 months or more previously, with a negative post-vasectomy semen analysis for sperm.
- Bilateral tubal ligation performed at least 6 months previously.
- Continuous use of an intrauterine device (non-hormone-releasing or hormone-releasing) for at least 90 days.
- Combined (estrogen and progestogen containing) or progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
  - injectable
  - implantable

NOTE: Hormonal contraceptives can be used as a highly effective method of contraception unless they're one of the prohibited medications as described in Section 5.12.3.3, as the efficacy of the hormonal contraceptives may be affected due to potential drug-drug interactions with DCC-2618.

Acceptable methods of contraception:

- Male and female condom with or without spermicide
- Barrier contraception (such as diaphragm, cervical cap or sponge) and spermicide
    - In countries where spermicide is not available, barrier contraception without spermicide is acceptable

Additional notes:

Acceptable methods of contraception listed above are examples. Local requirements may prohibit the use of some of these examples. Please contact the Sponsor with any questions.

- Female condom cannot be used with male condom (as a double method of contraception) due to risk of tearing.
- Male and female patients who are not sexually active at the time of screening must agree to follow the contraceptive requirements of this study if they become sexually active with a partner of the opposite sex.
- If applicable, additional contraception requirements may need to be followed according to local regulations and/or requirements.
- Male patients must not donate sperm after the first dose of study drug, throughout the study, and for 104 days following the last dose of study drug. They should seek advice on conservation of sperm prior to the first dose of study drug.
- Female patients and female partners of male patients must not plan to become pregnant during the study through 104 days following the last dose of study drug.
- Male patients whose female partner becomes pregnant through well-documented in vitro fertilization (donated sperm) or banked sperm (collected before the patient received study drug), must be compliant with the contraception requirements. In this scenario, the male patient must commit to using acceptable methods of contraception (to ensure there is no exposure of the fetus to study drug) for the duration of the study and until 104 days after the last dose of study drug.

Unique situations that may not fall within the above specifications must be discussed with the Sponsor.

If there is any question that a woman of childbearing potential or male patient will not reliably comply with the requirements for contraception, that patient must not be entered into the study.

6.11.10.2. Pregnancy

Patients must be counseled to inform the Investigator of any pregnancy that occurs during study treatment and for 104 days after the last dose of the study drug. An exception is made for pregnancies that occur 104 days after the last dose of study drug resulting from donated sperm or sperm banked before study drug exposure.

If a female patient becomes pregnant while participating in the study, study drug must be permanently discontinued immediately. If the female partner of a male patient becomes pregnant while participating in the study, the patient must notify the Investigator immediately. The male patient must to commit to use acceptable methods of contraception

(to ensure there is no exposure of the fetus to study drug) for the duration of the study and until 104 days after the last dose of study drug. The Investigator must notify the Sponsor and Worldwide Clinical Trials Pharmacovigilance (WCT PVG) within 1 business day of the site's knowledge of the patient's (or partner's) pregnancy.

If confirmed to be on active drug, the patient or partner must be followed until the end of the pregnancy and the infant must be followed for 1 year after the birth, provided informed consent is obtained. A separate ICF must be provided to explain these follow-up activities. Pregnancy itself does not constitute an AE.

6.11.11. Adverse Events

All AEs will be assessed, documented, and reported in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines. Section 7 outlines the definitions, collection periods, criteria and procedures for documenting, grading, and reporting AEs. A separate document that details AE eCRF completion guidelines for the Investigator, as well as training, will be provided.

6.11.12. Safety Follow Up

All patients must be followed for AEs; medications, including any anticancer treatments; and procedures until 30 days (+5 days) following the last dose of study drug.

6.12. Pharmacokinetics

6.12.1. Sample Collection

At the visits indicated in Table 1 (schedule of assessments) and Table 2 (schedule of assessments for crossover), blood samples will be collected for the determination of the concentrations of DCC-2618 and its metabolite, DP-5439. Pre-dose blood samples must be collected within 60 minutes before dosing and post dose blood samples must be collected ±30 minutes of the nominal time point. An unscheduled PK sample may be taken at the time of the onset of a new suspected, treatment-related AE when requested by the Sponsor.

Samples from the PK sampling will be kept frozen by the Sponsor or its designee until all analyses have been completed and then disposed of according to the Sponsor or designee standard operating procedures.

For each visit with a PK blood draw, a record of study drug administration must be collected as described in Section 5.2. The collection date and time that each PK blood sample is drawn must also be recorded.

Details on sample collection, processing, and shipping will be provided in a separate protocol-specific Laboratory Manual.

6.12.2. Sample Assessment

The following PK parameters will be calculated using non-compartmental methods of plasma DCC-2618 and metabolite DP-5439, obtained after single and repeated dose administration. The parameters will include, but may not be limited to C_{max}, T_{max}, AUC, and $T_{1/2}$.

6.13. Biomarkers and Pharmacodynamics

6.13.1. Sample Collection

Biomarker and PD samples will be collected according to the schedule in Table 1 (schedule of assessments) and Table 2 (schedule of assessments for crossover). A laboratory manual describing the details of obtaining, storing, and shipping the samples will be provided.

Remaining PD samples, including archival samples, will be stored for up to 15 years. These samples will be used for further analysis intended to address scientific questions related to study drug and/or cancer. A decision to perform such exploratory biomarker research studies will be based on data obtained from DCC-2618 clinical studies, new scientific findings related to the drug class or disease, and/or reagent and assay availability.

6.13.2. Sample Assessments

6.13.2.1. Tumor Tissue Samples

Mandatory archival and/or fresh tumor tissue samples will be collected and analyzed by a central laboratory to identify molecular alterations in KIT or PDGFRA or other kinases. At screening, an archival tumor tissue sample will be collected as long as no anticancer therapy was administered since the sample was collected. Fresh tumor tissue samples will only be collected if a patient qualifies for the study based on all other entry criteria and archival tissue is not available or not collected after the last anticancer therapy.

All Patients (optional): Additional tumor tissue samples may be collected for patients undergoing medical procedures including resection of metastases while on study or for patients that have disease progression if the patient consents and these samples will be used for further molecular testing of the cancer while treated with study drug.

6.13.2.2. Plasma Samples

Biomarker and PD plasma samples will be collected and analyzed by a central laboratory to evaluate mutations in KIT or PDGFRA and possibly other genes and their longitudinal frequency changes in cfDNA. Samples will be analyzed by NGS. Drug treatment effect on additional mutations of interest may also be evaluated.

6.14. Pharmacogenomic Measurements

6.14.1. Sample Collection

A pharmacogenomic sample will be collected at Cycle 1 Day 1 according to the schedule of study assessments in Table 1 (schedule of assessments). A laboratory manual describing the details of obtaining, storing, and shipping the sample will be provided.

6.14.2. Sample Assessment

A single whole blood sample will be collected and may be used to correlate study drug response and PK with individual genetic variation. The pharmacogenomic sample will be stored and analyzed by a central laboratory and may be stored for up to 15 years.

6.15. Healthcare Utilization

6.15.1. Healthcare Utilization Questionnaire (HCUQ)

The Healthcare Utilization Questionnaire was designed specifically for this study to collect data on the use of healthcare resources. It will be completed via a patient interview conducted

by the Investigator or designee participating in this study at the visits indicated in Table 1 (schedule of assessments) and Table 2 (schedule of assessments for crossover). The required time for completion is approximately 3-5 minutes. Certified translations of the HCUQ will be provided for sites in non-English-speaking countries.

The first section of the questionnaire deals with utilization of ambulatory healthcare services, with the staff member asking the patient about utilization of each of the services (emergency room, ambulance, primary care physician, specialist physician, counseling, other) and recording information as to whether the type of service had been used in the past 28 days (yes, no) and, if so, the number of times it was utilized. The second section proceeds in a similar way with data collection regarding the number of hospital admissions in the past 28 days, the length of stay, and the reason for each admission (disease/treatment related, other). The last section focuses on paid care provided in the patient's home by a nurse, home health aide, hospice worker, or another provider type in the last 28 days, with collection of whether service was provided and, if so, the number of days and the number of hours per day.

7. ADVERSE EVENT AND SERIOUS ADVERSE EVENT DOCUMENTATION, SEVERITY GRADING, AND REPORTING

7.1. Adverse Events

An **AE** is defined as any untoward medical occurrence in a patient administered a pharmaceutical product during the study, which does not necessarily have a causal relationship with the study drug. An AE can be any unfavorable and unintended sign (eg, including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug, whether or not it is considered to be study drug related. This includes any newly occurring event or previous condition that has increased in severity or frequency after the ICF is signed.

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was screened in the study and progression of underlying disease are not to be considered AEs unless the condition deteriorated in an unexpected manner during the study (eg, surgery was performed earlier than planned).

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, must not be reported as AEs. However, the medical condition for which the procedure was performed must be reported if it meets the definition of an AE.

Elective surgeries or procedures must not be reported as AEs, but must be documented on the appropriate eCRF page.

Each AE must be assessed immediately to determine if it meets the definition of serious (Section 7.8). If a serious adverse event (SAE) occurs, expedited reporting must follow local and international regulations, as appropriate.

7.2. Severity Assessment

The Investigator must determine and record the severity of all serious and non-serious AEs. The NCI-CTCAE, Version 4.03, must be used for grading the severity of AEs (Cancer Therapy Evaluation Program website; available at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

The severity of an AE that does not appear in the CTCAE scale must be determined according to Table 13.

Table 13: National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03 Severity Grading Scale

Grade 1 (Mild)	Experiences which are usually transient, requiring no special treatment, and do not interfere with the patient's daily activities.
Grade 2 (Moderate)	Experiences which introduce some level of inconvenience or concern the patient, and may somewhat interfere with daily activities, but are usually ameliorated by simple therapeutic measures (may include drug therapy).
Grade 3 (Severe)	Experiences which are unacceptable or intolerable, significantly interrupt the patient's usual daily activity, and require systemic drug therapy or other treatment.
Grade 4 (Life-threatening)	Experiences which cause the patient to be in imminent danger of death.
Grade 5 (Death)	Death related to AE.

7.3. Causality Assessment

The Investigator's assessment of relationship of the AE, if any to the study drug must be provided for all AEs. An Investigator's causality assessment is the determination of whether there is reasonable possibility that the study drug caused or contributed to an AE.

Relationship to study drug administration must be determined by the Investigator according to the following criteria in Table 14.

Table 14: Relationship to Study Drug Criteria

Related	There is an association between the event and the administration of study drug, a plausible mechanism for the event to be related to the study drug and causes other than the study drug has been ruled out, and/or the event re-appeared on re-exposure to the study drug.
Possibly Related	There is an association between the event and the administration of the study drug and there is a plausible mechanism for the event to be related to study drug, but there may also be alternative etiology, such as characteristics of the patient's clinical status or underlying disease.
Unlikely Related	The event is unlikely to be related to the study drug and likely to be related to factors other than the study drug.
Not Related	The event is related to an etiology other than the study drug (the alternative etiology must be documented in the study patient's medical record).

For the purpose of the safety analyses, all AEs that are classified as possibly related will be considered treatment-related events.

7.4. Study Drug Action Taken

The Investigator must classify the study drug action taken with regard to the AE. The action taken must be classified according to the categories shown in Table 15.

Table 15: Classification for Study Drug Action Taken with Regard to an Adverse Event

Classification	Definition
Dose Not Changed	Study drug dose not changed in response to an AE.
Dose Reduced	Study drug dose reduced in response to an AE.
Drug Interrupted	Study drug administration interrupted in response to an AE.
Drug Withdrawn	Study drug administration permanently discontinued in response to an AE.
Not Applicable	Action taken regarding study drug administration does not apply. "Not applicable" must be used in circumstances such as when the study drug had been completed before the AE began and no opportunity to decide whether to continue, interrupt, or withdraw study drug is possible.

7.5. Adverse Event Outcome

An AE must be followed until the Investigator has determined and provided the final outcome. The outcome must be classified according to the categories shown in Table 16.

Table 16: Classifications for Outcome of an Adverse Event

Classification	Definition
Recovered/Resolved	Resolution of an AE with no residual signs or symptoms.
Recovered/Resolved with Sequelae	Resolution of an AE with residual signs or symptoms.
Recovering/Resolving	Improvement of an AE
Not Recovered/Not Resolved (Continuing)	Either incomplete improvement or no improvement of an AE, such that it remains ongoing.
Fatal	Outcome of an AE is death. "Fatal" must be used when death is at least possibly related to the AE.
Unknown	Outcome of an AE is not known (e.g., a patient lost to follow-up).

7.6. Treatment Given

The Investigator must ensure adequate medical care is provided to patients for any AEs. In addition, the Investigator must describe whether any treatment was given for the AE. "Yes" is used if any treatment was given in response to an AE and may include treatments such as other medications, hospitalization, surgery, or physical therapy. "No" indicates the absence of any kind of treatment for an AE.

7.7. Additional Points to Consider for Adverse Events

7.7.1. Clinically Significant Assessments

Study assessments including laboratory tests, ECGs, physical examinations, and vital signs must be assessed and those deemed as clinically significant must be documented as an AE. When possible, a clinical diagnosis for the study assessment must be provided rather than the abnormal test result alone (eg, urinary tract infection, anemia). In the absence of a diagnosis, the abnormal study assessment itself may be listed as the AE (eg, bacteria in urine or decreased hemoglobin).

An abnormal study assessment is considered clinically significant if the patient has 1 or more of the following:

- Worsening, from baseline, concomitant signs or symptoms related to the abnormal study assessment
- Further diagnostic testing or medical/surgical intervention is required
- A change in the dose of study drug, if study drug is withheld, or discontinuation from study drug occurs

Repeat testing to determine whether the result is abnormal, in the absence of any of the above criteria, does not necessarily meet clinically significant criteria. The determination of whether the study assessment results are clinically significant must be made by the Investigator.

A laboratory abnormality judged to be Grade 4, in itself, may not constitute an SAE unless the clinical status of the patient indicates a life-threatening AE.

Symptoms of the disease under study must not be recorded as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease, including significant worsening unless the deterioration was unexpected, and are part of the efficacy data to be collected in the study.

7.8. Serious Adverse Events

An AE is considered serious if it meets any of the following:

- Results in death (regardless of cause, that occurs during participation in the study or occurs after participation in the study and is suspected of being a delayed toxicity due to administration of the study drug)
- Is life threatening (an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in congenital anomaly/birth defect
- Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes (ie, allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Clinical outcomes or symptoms related to progressive disease need to be reported as an SAE if they meet SAE criteria and occur within 30 days of the last study drug administration. They must be reported according to the diagnosis or symptom of event and not by the term “progressive disease.”

Clarification must be made between the terms "serious" and "severe," because they are not synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event, as in mild, moderate, or severe myocardial infarction. The event itself, however, may be of relatively minor medical significance, such as a severe headache. This is not the same as "serious," which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or functioning. Seriousness, not severity, serves as a guide for defining regulatory reporting obligations.

7.9. Adverse Events of Special Interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to study drug, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such AEs may require further investigation to characterize and understand them. Adverse events of special interest may be added or removed during a study by a protocol amendment.

The following AEs are considered AESIs:

- SCC
- Actinic keratosis
- Keratoacanthoma

7.10. Adverse Event Reporting Periods

The AE (including SAEs and AESIs) reporting period begins from the time that the patient provides informed consent through and including 30 days after the last administration of the study drug for all randomized patients. Patients who are not randomized will have AEs collected until the time of screen failure. Any SAE or AESI occurring after the reporting period must be promptly reported if a causal relationship to study drug is suspected.

If a patient begins a new anticancer therapy, the safety reporting period ends at the time the new treatment is started; however, death must always be reported when it occurs during the safety reporting period irrespective of intervening treatment.

7.11. Adverse Event, Serious Adverse Event, and Adverse Event of Special Interest Reporting Requirements

Each patient must be carefully monitored for the development of any AEs. This information must be obtained in the form of non-leading questions (eg, "How are you feeling?") and from signs and symptoms detected during each examination, observations of study personnel, and spontaneous reports from patients.

All AEs (serious and non-serious) spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures must be recorded. When possible, signs and symptoms indicating a common underlying pathology must be noted as 1 comprehensive event. Accompanying signs or symptoms (eg, abnormal laboratory values) must not be reported as additional AEs. If a diagnosis is unknown, one or more symptoms may be reported as separate AEs. If an underlying diagnosis is subsequently determined for the reported symptom(s), then the reported symptom(s) term(s) must be revised to be "attributed" or "due" to the diagnosis.

All SAEs and AESIs that occur within the reporting period, regardless of causality, must be reported by the Investigator to WCT PVG **within 24 hours** from the point in time when the Investigator becomes aware of the SAE or AESI. SAEs and AESIs must be followed until resolution, the condition stabilizes, or the Investigator and Sponsor agree that follow up is not required. For the purposes of study analysis, if the event has not resolved at the end of the study reporting period, it must be documented as ongoing. For purposes of regulatory safety monitoring, the Investigator is required to follow the event to resolution and report to the Sponsor the outcome of the event. Further instructions on reporting of SAEs will be provided in the Study Reference Manual.

If there are serious, unexpected, suspected adverse drug reactions (SUSARs) associated with the use of the study drug, the Sponsor or authorized designee will ensure that the appropriate regulatory agency(ies) and all participating investigators are notified on an expedited basis. In addition, the Sponsor or authorized designee will be responsible for notification of SUSARs to the ethics committee. It is the responsibility of the Investigator to promptly notify the local IRB/IEC/REB of SUSARs according to the institutional policy. An unexpected event is one that is not reported in the IB.

7.12. Abuse, Misuse, Overdose, and Medication Error

Occurrences of events of overdose, drug misuse, drug abuse and medication error must be reported to the Sponsor.

Abuse of a medicinal product: Persistent or sporadic, intentional excessive use of medicinal products, which is accompanied by harmful physical or psychological effects [DIR 2001/83/EC Art 1(16)].

Misuse: Intentional and inappropriate use of a medicinal product not in accordance with the prescribed or authorized dose, route of administration, and/or the indication(s) or not within the legal status of its supply.

Overdose: Administration of a quantity of study drug given per administration or per day, which is above the assigned dose.

Medication Error: An error made in prescribing, dispensing, administration, and/or use of the study drug. Medication errors are reportable to the Sponsor as defined below.

- The dispensing, administration and/or use of the unassigned study drug.
- The administration and/or use of an expired study drug.

Note: Cases of patients missing doses of the study drug are not considered reportable as medication errors.

AEs or SAEs associated with drug abuse, misuse, overdose, or medication error must be reported as appropriate (Section 7.1 and Section 7.8).

8. WITHDRAWAL AND REPLACEMENT OF PATIENTS

8.1. Withdrawal of Patients

A patient is free to withdraw from the study drug and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The Investigator is also free to terminate a patient's involvement in the study at any time if the patient's clinical condition warrants it. The primary reason for discontinuation or withdrawal of a patient from the study must be determined using the following categories:

- Adverse event
- Death
- Lost to follow-up
- Non-compliance with study drug
- Physician decision
- Pregnancy
- Confirmed progressive disease by Investigator assessment
- Confirmed progressive disease by independent radiologic review
- Protocol deviation
- Termination of site by Sponsor
- Termination of study by Sponsor
- Withdrawal by patient
- Any other reason that in the opinion of the Investigator, would justify removing the patient from the study, based on the best interest of the patient

If a patient voluntarily withdraws from the study, the Investigator should attempt to contact the patient to determine the reason(s) for discontinuation and request the patient return for an EOT Visit and Safety Follow up Visit. If a patient withdraws from the study for any reason other than withdrawal by the patient, an EOT Visit and Safety Follow up Visit must be conducted, and the patient must be followed for overall survival. . Patients must return all used, partially used, and unused study drug bottles.

8.2. Replacement of Patients

Patients will not be replaced in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Determination of Sample Size

The sample size selection of approximately 120 patients (n=80 DCC-2618, n=40 placebo) was based on considerations for powering of the primary endpoint, key secondary endpoint, detection of rare safety events and overall exposure to DCC-2618, and assuming 15% patient dropout. Patients will be randomized in a 2:1 ratio of DCC-2618 versus placebo.

This sample size [105 patients (n=70 DCC-2618, n=35 placebo) with 90 events (55 DCC-2618, 35 placebo) at the final analysis] will have at least 90% power to detect a difference in PFS between DCC-2618 and placebo assuming a median PFS of 4.5 months for DCC-2618 and 1 month for placebo. Moreover, this assumes 9 months of uniform recruitment and 6 additional months of follow-up (total patient follow-up of 15 months).

Furthermore, 105 patients (n=70 DCC-2618, n=35 placebo) will have approximately 80% power to detect a 0.2 difference in ORR assuming that the ORR for DCC-2618 = 0.22 and the ORR for placebo = 0.02.

In addition, a minimum sample size of 80 DCC-2618 patients allows adequate power to detect the incidence of rare safety events. A sample of 80 patients yields 95% probability that the study will reveal at least one occurrence of all safety events that occur in patients at a rate of 4.0% or greater. This in combination with the exposure to DCC-2618 from other studies conducted in this clinical program will meet the recommendations for overall exposure recommended by FDA.

9.2. Analysis Endpoints

9.2.1. Primary Endpoint

9.2.1.1. Efficacy

Progression-free survival based on independent radiologic review using modified RECIST (1; Appendix 17.1). Modified RECIST criteria includes:

- No lymph nodes chosen as target lesions; enlarged lymph nodes followed as non-target lesions;
- No bone lesions chosen as target lesions;
- PET not acceptable for radiological evaluation;
- A progressively growing new tumor nodule within a pre-existing tumor mass must meet the following criteria to be considered as unequivocal evidence of progression according to the modification of RECIST Version 1.1: (a) the lesion is at least 2 cm in size and definitively a new active GIST lesion (eg, enhancing with contrast or other criteria to rule out artefact); or (b) the lesion has to be expanding on at least 2 sequential imaging studies.

9.2.2. Secondary Endpoints

9.2.2.1. Key Secondary Endpoints

9.2.2.1.1. Efficacy

- ORR based on independent radiologic review

9.2.2.2. Additional Secondary Endpoints

9.2.2.2.1. Efficacy

- TTP based on independent radiologic review
- OS
- Time to best response
- PFS based on Investigator assessment
- QOL as determined by changes from baseline in EORTC-QLQ-C30 and EQ-5D-5L
- Disease control rate (DCR; CR + PR + SD) at 12 weeks

9.2.2.2.2. Safety

Safety endpoints that will be evaluated include TEAEs, AESIs, SAEs, dose reduction or discontinuation of study drug due to toxicity; and changes from baseline in ECOG PS, vital signs, ECG, LVEF, dermatologic examinations, and clinical laboratory parameters.

9.2.2.2.3. Pharmacokinetics

- Correlation of PK with efficacy/safety
- Population PK

9.2.3. Exploratory Endpoints

9.2.3.1. Efficacy

- PFS by Investigator assessment after dose escalation to DCC-2618 150 mg BID

9.2.3.2. Biomarkers and Pharmacodynamics

- Type and burden of mutations in plasma cfDNA
- Treatment effect of DCC-2618 on cfDNA mutation allele frequency
- Potential TKI-resistance mechanisms of GIST at time of progression
- Concordance between KIT, PDGFRA and other gene mutations in tumor and cfDNA

9.2.3.3. Healthcare Utilization

- Changes over time in healthcare utilization

9.3. Populations for Analysis

The following populations will be used in the analysis: Intent-to-treat (ITT), Safety, PK, and Per Protocol (PP).

The ITT population is defined as all patients who signed the informed consent and were randomized. The ITT population will be used for all efficacy analysis as a primary analysis set with treatment assignment based on randomization.

The Safety population is defined as all patients who have received at least 1 dose of study drug. The Safety population will be used for all safety analysis with treatment actually received.

The PK population will include all randomized subjects who received at least 1 dose of DCC-2618 and had at least 1 non-missing PK concentration in plasma reported for DCC-2618 or DP-5439.

A PP population may be included if there are patients in the ITT population who do not have protocol violations that are expected to compromise the efficacy and/or safety assessments (eg, patients enrolled who do not meet key eligibility criteria) during the study. Protocol violators resulting in exclusion from the PP population will be identified and documented prior to database lock.

9.4. Procedures for Handling Missing, Unused, and Spurious Data

All available data will be included in data listings.

Algorithms for imputing partial or missing dates are shown in Table 17. If a period determination cannot be made for an adverse event, it will be attributed to the randomized blinded period, with missing dates imputed as explained in Table 18. Adverse event end dates are imputed to facilitate calculation of AE duration.

Table 17: Partial or Missing Date Algorithms

Variable	Missing Day	Missing Day, Month	Missing Day, Month, Year
Date of Last Therapy/Date of Initial Diagnosis	Assign 1	Assign January 1 if prior to date of informed consent, otherwise use date of informed consent	Missing (do not impute)
Adverse Event/Start Date	Assign first day of month unless it is the year/month of first dose of study medication. Otherwise, assign date of first dose of study medication or AE end date (if not missing) whichever is earlier.	Assign January 1 unless the year is year of first dose of study medication Otherwise, assign date of first dose of study medication or AE end date (if not missing) whichever is earlier.	Assign date first dose of study medication.
Adverse Event End Date	Assign the last day of the month or end of study date, whichever is earlier.	Assign December 31 or end of study date, whichever is earlier.	If ongoing, end date is missing. Otherwise, assign end of study date.

Table 18: Imputation Rules for Questionnaires

Questionnaire	Number of items missing < half	Number of items missing > half
EORTC-QLQ-C30	No imputation for missing	Impute missing values by using the average score from the patients with non-missing values from within the same randomization strata

9.5. Interim Analyses

No interim analysis for efficacy will be performed for this study. An IDMC will be used to review safety data periodically throughout the course of this study (see Section 10.1 for further details).

9.6. Adjustment for Multiple Comparisons

To control family wise type-I error, the hypothesis tests for treatment difference will be performed at two-sided 0.05 level of significance sequentially in the following order:

1. The primary endpoint PFS
2. The key secondary endpoint ORR
3. OS
4. QOL as determined by changes from baseline to Day 1 of cycle 2 in EORTC-QLQ-C30 Role function and Physical function (each at 0.025 level significance)

Once a hypothesis test is nonsignificant at alpha=0.05 level, the remaining analyses will be viewed as descriptive.

9.7. Blinding

Prior to the unblinding of study data, the Sponsor will approve a comprehensive statistical analysis plan (SAP).

Where required, safety personnel at the Sponsor or designee may be unblinded to a patient's study drug assignment to meet reporting requirements to regulatory agencies. In addition, the Investigator, patient, Sponsor, and study team will be unblinded at the time the patient has disease progression by modified RECIST based on independent radiology review.

Additional Sponsor representatives may be unblinded to some data for the purposes of ensuring adequacy of study conduct, including proper distribution of study drug.

At no point in time before official full study unblinding will any aggregate efficacy and safety analyses be conducted by the Sponsor or Sponsor representatives, unless there is explicit permission to do so, for instance high level efficacy assessment for the purposes of IDMC review to determine the adequacy of the risk/benefit profile of the drug as it pertains to the conduct of the clinical trial.

Upon determining the results based on the primary PFS analysis, all remaining patients will be unblinded to their treatment assignment and patients assigned to placebo will be allowed to cross-over to active therapy.

9.8. Statistical Methods

9.8.1. General Methods

Data collected in this study will be documented using summary tables and patient data listings. Continuous variables will be summarized using descriptive statistics (number of patients, mean, median, standard deviation, minimum, and maximum). Categorical variables will be summarized using frequencies and proportions. Time-to-event data will be summarized via Kaplan-Meier (KM) methodology using the 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals.

Unless specified otherwise, baseline measurements must be the most recent value prior to receiving the first dose of study medication. If an assessment is not available, then the last assessment prior to that visit would be used.

Medical history, adverse events, and concurrent procedures will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary.

This study will be broken into 2 periods: the randomized blinded period and the open-label portion which occurs after the study treatment unblinding at the time of disease progression based on the independent radiologic review.

The data cut-off for the primary analysis will occur when 90 PFS events have occurred. It is expected that the final analysis will occur within 6 months after the last patient is enrolled into the trial.

Unless specified, the ITT population is used for efficacy analysis and the Safety population is used for the safety analysis.

9.8.2. Disposition of Patients

Patient disposition will be summarized overall for all patients who entered the study (ie, signed the informed consent for the study). The number and proportion of patients who entered the open-label portion of the study will be displayed. In addition, the number of patients in each population (ITT, Safety, and PP if applicable) and patients were removed from a population. The number and proportion of patients who complete the study, as well as those who discontinue the study will be summarized along with the reason for discontinuation.

9.8.3. Demographic and Baseline Characteristics

Demographic and baseline characteristics at study entry will be summarized for the ITT, Safety, and PP populations.

Medical history will be summarized overall for the Safety population.

9.8.4. Extent of Exposure

The total number of patients who received study medication will be summarized by n and percentage. In addition, the number of cycles received will be displayed using continuous descriptive statistics. These analyses will be performed for the Safety population.

9.8.5. Efficacy Analysis

9.8.5.1. Primary Endpoint: Progression-free Survival Analysis

The primary endpoint of PFS (reported in weeks) is defined as the interval between the date of randomization and the earliest documented evidence of disease progression based on the independent radiologic review, or death due to any cause. Patients who undergo surgical resection of target or non-target lesions, who have received other anticancer treatments, or patients who do not have a documented date of progression or death due to any cause will be censored at the date of the last assessment. Analysis for PFS will be stratified by the randomization stratification factors [prior lines of therapy (3 versus ≥4) and ECOG (0 versus 1 or 2)]. The p-value will be from a 2-sided stratified Log-rank test at 0.05 significant level for evaluation of treatment difference. Point estimate of hazard ratio will be obtained from a

Cox regression model with the treatment and the randomization stratification factors as fixed factors and it's 95% CI will be obtained using the Wald method.

Analysis will be using the ITT population as the primary analysis and PP as supportive. Progression-free survival will have sensitivity analyses performed which will be further detailed in the SAP.

9.8.5.2. Key Secondary Endpoint

The key secondary endpoint is ORR.

9.8.5.2.1. Objective Response Rate Analysis

Objective response rate is defined as the proportion of patients with a confirmed CR or PR based on the independent radiologic review. This analysis will be performed in the ITT population as the primary analysis and the PP population as supportive analysis. To be assigned a status of a CR or PR, changes in tumor measurements must be confirmed by repeat assessments that must be performed at least 4 weeks after the criteria for response are first met. Patients with unknown or missing response will be treated as non-responders, that is, they will be included in the denominator when calculating the proportion. Time to confirmed response (CR or PR) (reported in weeks) is defined as the interval between the date of first dose of study medication and the earliest date of first documented confirmed CR or confirmed PR. Patients who do not have a confirmed PR or CR will be censored at the date of the last adequate assessment. An unstratified two-sided Fisher's Exact test at a 0.05 significance level will be used to investigate statistical differences between treatment groups. A 95% confidence interval of treatment rate difference in ORR will be calculated by the Wald method.

9.8.5.3. Secondary Endpoints

9.8.5.3.1. Time to Tumor Progression

The secondary endpoint of TTP (reported in weeks) is defined as the interval between the date of randomization and the earliest documented evidence of disease progression based on the independent radiologic review. Patients who undergo surgical resection of target or non-target lesions, who have received other anticancer treatments, who do not have a documented date of progression or death due to any cause, or who die prior to tumor progression will be censored at the date of the last assessment. P-value for treatment difference will be obtained using the log rank test. Hazard ratio will be from a Cox regression model and it's 95% confidence intervals will use Wald method.

9.8.5.3.2. Overall Survival

Overall survival (reported in weeks) is defined as the interval between the date of randomization and date of death from any cause. Patients who are still alive or who are lost to follow-up will be censored at the date of last contact. Differences between treatment groups will be evaluated using a model similar to that used for PFS.

9.8.5.3.3. Time to Best Response Analysis

The time to best response, as defined by the independent radiologic review, will be summarized and displayed using KM methods in a manner similar to the PFS analysis as described above.

9.8.5.3.4. Progression-free Survival based on Investigator Assessment

PFS (reported in weeks) is defined as the interval between the date of randomization and the earliest documented evidence of disease progression based on Investigator assessment, or death due to any cause. Patients who undergo surgical resection of target or non-target lesions, who have received other anticancer treatments, or patients who do not have a documented date of progression or death due to any cause will be censored at the date of the last assessment. Differences between treatment groups will be evaluated using a model similar to that used for the primary endpoint. .

9.8.5.3.5. EORTC-QLQ-C30

The EORTC-QLQ-C30 will be summarized by scale. In all scales, a high scale score represents a higher response level. The scoring for this questionnaire will be done in 2 steps. The first step is to estimate the average of the items that contribute to the scale. This will be considered the raw score for the scale. After the raw score has been calculated, a linear transformation will be used to standardize the raw score, so that scores range from 0 to 100. An analysis of covariance with treatment, KIT/PDGFRA fourth line/KIT/PDGFRA fifth line/PDGFRA D842V status, and ECOG status at baseline will be performed.

9.8.5.3.6. EQ-5D-5L

The EQ-5D-5L will be summarized overall by n and percentage for each level of each dimension. The Cochran–Mantel–Haenszel test will be used to test differences between DCC-2618 and placebo. The EQ-VAS will be summarized using continuous descriptive statistics.

9.8.5.3.7. Disease Control Rate Analysis

Disease control rate will be calculated and summarized with n and percentage at 12 weeks. Disease control will be defined as having a response (complete or partial) or stable disease. This analysis will be performed by time point. Fisher's Exact test will be used to investigate statistical differences between treatment groups and the Cochran-Mantel-Haenszel (CMH) will be utilized to assess the effect of strata.

9.8.5.4. Exploratory endpoint

9.8.5.4.1. Progression-free Survival by Investigator Assessment after Dose Escalation to DCC-2618 150 mg BID

Progression-free survival (reported in weeks) after dose escalation to 150 mg BID is defined as the interval between the date of first dose of DCC-2618 150 mg BID and the earliest documented evidence of disease progression after dose escalation to 150 mg BID, or death due to any cause. Patients who undergo surgical resection of target or non-target lesions, who have received other anticancer treatments, or patients who do not have a documented date of progression or death due to any cause will be censored at the date of the last assessment post the first dose of DCC-2618 150 mg BID or if there are no assessments post the first dose, the first dose will be used as the censor date.

9.8.6. Safety Analysis

9.8.6.1. Adverse Events

Adverse events will be summarized utilizing the number and proportion of patients overall and by period (randomized/open-label), system organ class and preferred term for the Safety population. All tables will only include TEAEs, where treatment emergent is defined as any AE that occurs after administration of the first dose of study drug and through 30 days after the last dose of study drug, but listings will include all AEs.

Adverse event toxicity grade will be classified using NCI-CTCAE Version 4.03 criteria (See Table 13). If a patient has multiple occurrences of the same system organ class (SOC) or preferred term, then only the most severe event will be summarized in the tables for that SOC and preferred term. Adverse events of ≥Grade 3 will also be summarized. A missing toxicity grade will not be imputed.

The AE analysis will be repeated for SAEs, AEs leading to dose reduction or discontinuation, and AESIs.

No formal hypothesis-testing analysis of AE incidence rates will be performed.

9.8.6.2. Eastern Cooperative Oncology Group Performance Status

Assessments will be summarized overall by time point utilizing continuous descriptive statistics. In addition, the change from baseline will be summarized for continuous parameters. For categorical parameters, the n and percentage will be displayed. No formal hypothesis-testing analysis will be performed.

9.8.6.3. Vital Signs

Assessments will be summarized overall by time point utilizing continuous descriptive statistics. In addition, the change from baseline will be summarized for continuous parameters. For categorical parameters, the n and percentage will be displayed. No formal hypothesis-testing analysis will be performed.

9.8.6.4. Echocardiogram/Multigated Acquisition Scans

Assessments will be summarized overall by time point utilizing continuous descriptive statistics. In addition, the change from baseline will be summarized for continuous parameters. For categorical parameters, the n and percentage will be displayed. No formal hypothesis-testing analysis will be performed.

9.8.6.5. Dermatologic assessments

Dermatologic assessments will be summarized by n and percent. No formal hypothesis-testing analysis will be performed.

9.8.6.6. Clinical Laboratory Parameters

Assessments will be summarized overall by time point utilizing continuous descriptive statistics. In addition, the change from baseline will be summarized for continuous parameters. For categorical parameters, the n and percentage will be displayed. No formal hypothesis-testing analysis will be performed.

9.8.7. Pharmacokinetic Analysis

Pharmacokinetic concentrations will be summarized utilizing continuous descriptive statistics.

9.8.8. Biomarker and Pharmacodynamic Analysis

The Mann-Whitney U test will be used to examine the statistical difference between treatment groups in terms of treatment effect of DCC-2618 on cfDNA mutation frequency over all time point tested. No formal hypothesis-testing analysis will be performed.

9.8.9. Pharmacogenomic Analysis

Pharmacogenomic analysis to explore the impact of variations in genes encoding for drug metabolism enzymes and drug transporters on patient's response to study drug.

9.8.10. Healthcare Utilization

Data collected on the HCUQ will be summarized using n and percentage or continuous descriptive statistics as appropriate based on the item collected. These data will be compared between treatment groups over time as applicable using the appropriate statistical test.

9.8.11. Procedures for Reporting Deviations to Original Statistical Analysis Plan

All deviations from the original SAP will be provided in the final clinical study report.

10. STUDY COMMITTEES

10.1. Independent Data Monitoring Committee

An IDMC will monitor the safety data from this study on a periodic basis to help ensure the ongoing safety of study patients. The IDMC will consist of an experienced biostatistician and two qualified clinicians, who are not employees of the Sponsor, with combined scientific expertise in general oncology and GIST and practical experience conducting clinical studies and monitoring safety and efficacy of clinical studies. The IDMC or Sponsor may request an ad hoc meeting for any reason, including significant unexpected safety event, unplanned unblinding of study results, follow-up of an observation during a planned IDMC meeting, or a report external to the study, such as publication of study results from a competing product.

The IDMC objectives and operational details will be defined in a separate document (IDMC Charter), which will be finalized before the first patient is randomized in the study.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. Study Site Monitoring Visits

During study conduct, the Sponsor or its agent will conduct periodic monitoring visits to ensure that the protocol and GCPs are being followed. The monitors will review source documents to confirm that the data recorded on eCRFs is accurate. The Investigator and institution will allow the Sponsor's monitors or designees and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the IRB/IEC/REB, and/or to quality assurance audits performed by the Sponsor, or companies working with or on behalf of the Sponsor, and/or to inspection by appropriate regulatory authorities.

It is important that the Investigator and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11.2. Protocol Compliance

The Investigator must conduct the study in compliance with the protocol provided by the Sponsor and given approval/favorable opinion by the IRB/IEC/REB and the appropriate regulatory authority(ies). Modifications to the protocol must not be made without agreement between both the Investigator and the Sponsor. Changes to the protocol will require written IRB/IEC/REB and the appropriate regulatory authority(ies) approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC/REB may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval/favorable opinion of the IRB/IEC/REB. The Sponsor must ensure that all protocol modifications are submitted to the regulatory authority(ies) in accordance with the governing regulations.

If other unexpected circumstances arise that require deviation from protocol-specified procedures, the Investigator must consult with the Sponsor (and IRB, IEC, or REB, as required) to determine the appropriate course of action.

The site must document all protocol deviations in the patient's source documents. In the event of a significant deviation, the site must notify the Sponsor (and IRB, IEC, or REB, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the patient, or confound interpretation of primary study assessments.

12. DATA HANDLING AND RECORD KEEPING

12.1. Electronic Case Report Form

The Sponsor or designee will provide the study sites with secure access to and training on the electronic data capture application sufficient to permit site personnel to enter or correct information in the eCRFs on the patients for which they are responsible.

An eCRF is required and must be completed for each randomized patient. The Investigator has ultimate responsibility for the accuracy, authenticity, and timely collection and reporting of all clinical, safety, and laboratory data entered on the eCRFs and any other data collection forms. Source documentation supporting the eCRF data must indicate the patient's participation in the study and must document the dates and details of study procedures, AEs, other observations, and patient status.

The Investigator, or designated representative, must complete the eCRF as soon as possible after information is collected.

The audit trail will show the user's identification information and the date and time of the any correction. The eCRFs must be signed electronically by the Investigator to attest that the data contained on the eCRFs, including any changes made to the eCRFs, is correct and endorse the final submitted data for the patients for whom the Investigator is responsible.

The completed eCRFs are the sole property of the Sponsor and must not be made available in any form to third parties, except for authorized representatives of the Sponsor or appropriate regulatory authorities, without written permission from the Sponsor.

The Sponsor will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disc or other electronic media will be provided to the site for placement in the Investigator's study file.

12.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, eCRFs and hospital records), all original signed informed consent forms, eCRFs, SAE forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records must be retained by the Investigator according to the ICH, local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the Investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), the Sponsor must be prospectively notified. The study records must be transferred to a designee acceptable to the Sponsor, such as another Investigator, another institution, or to the Sponsor. The Investigator must obtain the Sponsor's written permission before disposing of any records, even if retention requirements have been met.

13. ETHICS

13.1. Ethical Conduct of the Study

The study will be conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the General Assembly of the World Medical Association (31).

In addition, the study will be conducted in accordance with the protocol, ICH GCP, and applicable local regulatory requirements and laws.

The Investigator must ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 21 CFR Part 50, 21 CFR Part 54, 21 CFR Part 56, 21CFR Part 312, 21 CFR Part 314 and ICH GCP E6.

13.2. Patient Information and Consent

All parties must ensure protection of patient personal data and must not include patient names on any Sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, the Sponsor must maintain high standards of confidentiality and protection of patient personal data.

The informed consent form must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC/REB and the Sponsor before use.

The Investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation. The Investigator, or a person designated by the Investigator, must obtain written informed consent from each patient or the patient's legally acceptable representative before any study-specific activity is performed. The Investigator must retain the original of each patient's signed consent form.

13.3. IRB/IEC/REB

It is the responsibility of the Investigator to have prospective approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents, (eg, recruitment advertisements, if applicable) from the IRB/IEC/REB. All correspondence with the IRB/IEC/REB must be retained in the Investigator Site File.

The only circumstance in which an amendment may be initiated prior to IRB/IEC/REB approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the Investigator must notify the IRB/IEC/REB and the Sponsor in writing immediately after the implementation.

13.4. Patient Confidentiality

The Sponsor and designees affirm and uphold the principle of the patient’s right to protection against invasion of privacy. Throughout this study, a patient’s source data must only be linked to the Sponsor’s clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited patient attributes, such as sex, age, or date of birth may be used to verify the patient and accuracy of the patient’s unique identification number.

To comply with ICH GCP and to verify compliance with this protocol, the Sponsor requires the Investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA), the Sponsor's designated auditors, and the appropriate IRBs and IECs to review the patient's original medical records (source data or documents), including, but not limited to, any genetic/genomic data the patient might have from testing done prior to entering the study, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a patient's study participation, and autopsy reports. Access to a patient's original medical records requires the specific authorization of the patient as part of the informed consent process (Section 13.2).

Copies of any patient source documents that are provided to the Sponsor must have certain personally identifiable information removed (ie, patient name, address, and other identifier fields not collected on the patient's eCRF).

13.5. Reporting of Safety Issues or Serious Breaches of the Protocol or International Conference on Harmonization Good Clinical Practice

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority, or if the Investigator is aware of any new information which might influence the evaluation of the benefits and risks of the study drug, the Sponsor must be informed immediately.

In addition, the Investigator must inform the Sponsor immediately of any urgent safety measures taken by the Investigator to protect the study patients against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that comes to the attention of the Investigator.

13.6. Liability and Insurance

The Sponsor has subscribed to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards.

14. STUDY TERMINATION

When the Sponsor is aware of information on matters concerning the quality, efficacy, and safety of the study drug, as well as other important information that may affect proper conduct of the clinical study, the Sponsor may discontinue the clinical study and send a written notice of the discontinuation along with the reason to the Investigator.

If an Investigator intends to discontinue participation in the study, the Investigator must immediately inform the Sponsor of the discontinuation and the reason for it.

14.1. Criteria for Suspension or Premature Termination of the Study

Criteria for either temporary suspension or premature termination of the study include:

1. New information regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for patients participating in the study.
2. Significant violation of GCP that compromises the ability to achieve the primary study objectives or compromises patient safety.
3. The Sponsor may suspend or prematurely terminate the study for reasons not related to the conduct of the study.

14.2. Criteria for Premature Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the site (including the Investigator) is found to be in significant violation of GCP, protocol, contractual agreement, or is unable to ensure adequate performance of the study.

14.3. Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

In the event that the Sponsor elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the Sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

15. PUBLICATION OF STUDY RESULTS

Any and all scientific, commercial, and technical information disclosed by the Sponsor in this protocol or elsewhere must be considered the confidential and proprietary property of the Sponsor. The Investigator shall hold such information in confidence and shall not disclose the information to any third party except to such of the Investigator's employees and staff as have been made aware that the information is confidential and who are bound to treat it as such and to whom disclosure is necessary to evaluate that information. The Investigator shall not use such information for any purpose other than determining mutual interest in performing the study and, if the parties decide to proceed with the study, for the purpose of conducting the study.

The Investigator understands that the information developed from this clinical study will be used by the Sponsor in connection with the development of the study drug and therefore may be disclosed as required to other clinical investigators, business partners and associates, the FDA, and other government agencies. The Investigator also understands that, to allow for the use of the information derived from the clinical study, the Investigator has the obligation to provide the Sponsor with complete test results and all data developed in the study.

No publication or disclosure of study results will be permitted except under the terms and conditions of a separate written agreement between the Sponsor and the Investigator and/or the Investigator's institution.

16. REFERENCES

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17. APPENDICES

17.1. Modified Response Evaluation Criteria in Solid Tumors (RECIST)

Modified RECIST criteria includes:

- No lymph nodes chosen as target lesions; enlarged lymph nodes followed as non-target lesions;
- No bone lesions chosen as target lesions;
- Positron emission tomography (PET) not acceptable for radiological evaluation;
- A progressively growing new tumor nodule within a pre-existing tumor mass must meet the following criteria to be considered as unequivocal evidence of progression according to the modification of RECIST Version 1.1: (a) the lesion is at least 2 cm in size and definitively a new active GIST lesion (eg, enhancing with contrast or other criteria to rule out artefact); or (b) the lesion has to be expanding on at least 2 sequential imaging studies.

Source: Demetri GD, Jeffers M, Reichardt P, Kang Y-K, Blay J-Y, Rutkowski P, et al. Mutational analysis of plasma DNA from patients (pts) in the phase III GRID study of regorafenib (REG) versus placebo (PL) in tyrosine kinase inhibitor (TKI) refractory GIST: Correlating genotype with clinical outcomes. J Clin Oncol 31, 2013 (suppl; abstr 10503).

17.2. Healthcare Utilization Questionnaire

Healthcare Utilization Questionnaire Instructions

Administration: The questionnaire should be completed via a patient interview by a healthcare provider participating in the study.

Healthcare Utilization Questionnaire

A. Healthcare Visits

Other than what was required for this study, did you use any of the following health care services during the last 28 days (4 weeks)?	Yes No	Number during the last 28 days
Emergency room visit	□ □	
Use of an ambulance	□ □	
Outpatient primary care physician visit	□ □	
Outpatient specialist visit (e.g., oncologist, surgeon)	□ □	
Outpatient counseling visit (e.g., psychiatrist, psychologist, therapist, mental health specialist)	□ □	
Other	□ □	

B. Inpatient Visits

Did you spend any days in the following facilities during the last 28 days (4 weeks)?	Yes No	Length of Stay (days)	Reason for Stay
Inpatient hospital	□ □		□ Disease/treatment related □ Other
Rehabilitation facility	□ □		□ Disease/treatment related □ Other
Hospice facility	□ □		□ Disease/treatment related □ Other
Respite care (eg, caregiver relief)	□ □		□ Disease/treatment related □ Other
Skilled nursing facility/nursing home	□ □		□ Disease/treatment related □ Other

C. Care in the home

Did any healthcare worker provide services to you in your home during the last 28 days (4 weeks)?	Yes No	Number of days	Number of hours per day
Nurse	□ □		
Home health aide	□ □		
Hospice worker	□ □		
Other	□ □		