Trial ID: 2618-03-002 INTRIGUE

Document: Protocol

Official Title: A Phase 3, Interventional, Randomized, Multicenter, Open--label Study of DCC-2618 vs Sunitinib in Patients with Advanced Gastrointestinal Stromal Tumors after Treatment with Imatinib

ClinicalTrial.gov NCT Number: NCT03673501

Approval Date: 23 Oct 2020

CLINICAL STUDY PROTOCOL

Protocol DCC-2618-03-002 (intrigue)

A Phase 3, Interventional, Randomized, Multicenter, Open-Label Study of DCC-2618 vs Sunitinib in Patients with Advanced Gastrointestinal Stromal Tumors after Treatment with Imatinib

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: 200 Smith Street Waltham, MA 02451 [redacted]
	Research Facility: 643 Massachusetts St., Suite 200 Lawrence, KS 66044 [redacted]
IND Number:	[redacted]
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SPONSOR SIGNATURE

Signature Page for DCC-CLIN-000255 v1.0

Approval	[redacted] 23-Oct-2020 19:45:31 GMT+0000

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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, Inc. 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, Randomized, Multicenter, Open-Label Study of DCC-2618 vs Sunitinib in Patients with Advanced Gastrointestinal Stromal Tumors after Treatment with Imatinib (intrigue)
Protocol Number:	DCC-2618-03-002
Study Phase:	3
Study Centers:	Approximately 125 centers globally
Number of Patients Planned:	426 patients (213 randomized to DCC-2618 and 213 randomized to sunitinib)
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 previously received first-line therapy with imatinib Key Secondary Objectives: • To assess objective response rate (ORR) by independent radiologic review using modified RECIST (mRECIST) criteria • To assess Overall Survival (OS) Other Secondary Objectives: • To assess the quality-of-life (QOL) during treatment as measured by: o EORTC QLQ-C30 o Dermatology Life Quality Index (DLQI) o GP5 question from the FACT-G (burden of side-effects) • To assess Time to Tumor Progression (TTP) by independent radiologic review • To assess efficacy parameters, including disease control rate (DCR), PFS based on Investigator assessment, and efficacy based on Choi criteria by independent radiologic review • To assess the PK/PD relationship of DCC-2618 • To compare the safety profile of DCC-2618 to the safety profile of sunitinib Exploratory Objectives: • To assess the QOL during treatment as measured by: o Memory and concentration items from the PRO-CTCAE library o EQ-5D-5L

	• To assess Progression Free Survival on the next line therapy (PFS2) based on local assessment • To evaluate potential biomarkers in blood or tumor tissue which might predict response to DCC-2618 o To understand potential resistance mechanisms to DCC-2618 in GIST o To characterize KIT and PDGFRA mutations at baseline and DCC-2618-driven longitudinal mutant allele frequency changes in plasma • To assess healthcare utilization
Study Design:	This is a 2-arm, randomized, open-label, international, multicenter study comparing the efficacy of DCC-2618 to sunitinib in GIST patients who progressed on or were intolerant to first-line anticancer treatment with imatinib. Approximately 426 patients will be randomized in a 1:1 ratio to DCC-2618 150 mg once daily (QD) or sunitinib 50 mg QD, 4 weeks on, 2 weeks off. [redacted] Randomization will be stratified by: • Mutational Status: KIT exon 9 mutation; KIT exon 11 mutation; KIT/PDGFRA WT; or other KIT (absence of exon 9 or 11)/PDGFRA mutations • Intolerance to imatinib (Yes or No) The primary endpoint of the study will be evaluated using the modified Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 – GIST-specific (hereafter referred to as "mRECIST") based on independent radiologic review. Upon disease progression by mRECIST based on independent radiologic review, patients will discontinue their assigned treatment.
Study Population: Inclusion Criteria	Patients must meet all of the following criteria to be eligible to enroll in the study: 1. Patients ≥ 18 years of age at the time of informed consent. 2. Histologic diagnosis of GIST and must be able to provide an archival tumor tissue sample, otherwise, a fresh biopsy is required. 3. Molecular pathology report with mutational status of KIT/PDGFRA must be available. Mutation status must be identified using a tissue based PCR/sequencing assay. Molecular pathology report with mutation status of KIT/PDGFRA must be provided to the Sponsor for review prior to randomization. If the molecular pathology report is not available or insufficient, an archival tumor tissue sample or fresh biopsy is required for mutation status confirmation by the central laboratory prior to randomization.

	4. Patients must have progressed on imatinib or have documented intolerance to imatinib. Imatinib treatment must have been discontinued 10 days prior to the first dose of study drug. All prior imatinib treatment will count as one line of therapy (e.g. adjuvant imatinib and dose escalation of imatinib). 5. Eastern Cooperative Oncology Group (ECOG) PS of ≤ 2 at screening. 6. Female patients of childbearing potential must have a negative serum beta-human chorionic gonadotrophin (β-hCG) pregnancy test at screening and 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 contraception requirements outlined in Section 6.11.9. 8. Patients must have at least 1 measurable lesion according to mRECIST Version 1.1 (non-nodal lesions must be ≥ 1.0 cm in the long axis or ≥ double the slice thickness in the long axis) within 21 days prior to the first dose of study drug. 9. Adequate organ function and bone marrow reserve as indicated by the following central laboratory assessments performed at screening: a. Absolute Neutrophil Count (ANC) ≥ 1000/µL b. Hemoglobin ≥ 8 g/dL c. Platelet count ≥ 75,000/µL d. Total bilirubin ≤ 1.5 x the upper limit of normal (ULN) e. Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3 x ULN (≤ 5x ULN in the presence of hepatic metastases) f. Creatinine clearance ≥ 50 ml/min based on Cockcroft Gault estimation g. Prothrombin time (PT), international normalized ratio (INR) and partial thromboplastin time (PTT) ≤ 1.5 x ULN. Patients on a stable regimen of anticoagulant therapy for at least one month prior to the first dose of study drug 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. 10. Resolution of all toxicities from prior therapy to ≤ Grade 1 (or patient baseline) within 1 week prior to the first dose of study drug (excluding alopecia and ≤ Grade 3 clinically asymptomatic lipase, amylase, and creatine phosphokinase (CPK) laboratory abnormalities). 11. The patient is capable of understanding and complying with the protocol and the patient has signed the informed consent document. Signed informed consent form (ICF) must be obtained before any study-specific procedures are performed and the patient must agree to not participate in any other interventional clinical trial while on

	treatment in this clinical trial. Participation in a noninterventional study (including observational studies) is permitted.
Exclusion Criteria	Patients meeting any of the following criteria will be excluded from the study: 1. Treatment with any other line of therapy in addition to imatinib for advanced GIST. Imatinib-containing combination therapy in the first-line setting is not allowed. 2. Patients with a prior or concurrent malignancy whose natural history or treatment have the potential to interfere with the safety or efficacy assessment of this clinical trial are not eligible. For example, patients receiving adjuvant cancer treatment are not eligible if those medications are potentially active against GIST or excluded per protocol. NOTE: Patients with a history of breast cancer, requiring continued hormonal treatment (e.g. anti-estrogen or an aromatase inhibitor) may continue treatment. Patients with a history of prostate cancer, requiring continued support with luteinizing hormone-releasing hormone (LHRH) agonists, with or without androgens, may continue treatment. NOTE: Patients may not be part of an ongoing or have prior participation in an investigational drug study within 30 days of screening. 3. Patient has known active central nervous system metastases. 4. New York Heart Association class II-IV heart disease, myocardial infarction within 6 months of cycle 1 day 1, active ischemia or any other uncontrolled cardiac condition such as angina pectoris, clinically significant cardiac arrhythmia requiring therapy, uncontrolled hypertension or congestive heart failure. 5. Left ventricular ejection fraction (LVEF) < 50% at screening. 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 (e.g. deep vein thrombosis) or pulmonary arterial events (e.g. pulmonary embolism) within 1 month before the first dose of study drug. Patients on stable anticoagulation therapy for at least one month are eligible. 8. 12-lead electrocardiogram (ECG) demonstrating QT interval corrected (QTc) by Fridericia's formula > 450 ms in males or > 470 ms in females at screening or history of long QT syndrome. 9. Use of strong or moderate inhibitors or inducers of cytochrome P450 (CYP) 3A4, including certain herbal medications (e.g. St. John's Wort) within 14 days or 5 x the half-life (whichever is longer) prior to the first dose of study drug, and consumption of grapefruit or grapefruit juice within 14 days 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/induce CYP3A4 enzymes. See Section 5.12.3.2. 10. 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 US Food and Drug Administration's (FDA) website for inhibitors and substrates (https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm). See Section 5.12.3.2 11. Major surgeries (e.g. abdominal laparotomy) within 4 weeks of the first dose of study drug. All major surgical wounds must be healed and free of infection or dehiscence before the first dose of study drug. 12. 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. 13. Known human immunodeficiency virus or hepatitis C infection only if the patient is taking medications that are excluded per protocol (Section 5.12.3.2), active hepatitis B, or active hepatitis C infection. 14. If female, the patient is pregnant or lactating. 15. Known allergy or hypersensitivity to any component of the study drug. Patients with history of Stevens-Johnson syndrome on a prior tyrosine kinase inhibitor (TKI) are excluded. 16. Gastrointestinal abnormalities including, but not limited to: a. inability to take oral medication b. malabsorption syndromes c. requirement for intravenous (IV) alimentation 17. Any active bleeding excluding hemorrhoidal or gum bleeding.
Study Drug:	DCC-2618 or sunitinib
Formulation:	DCC-2618 tablets or sunitinib capsules
Dose:	DCC-2618: 150 mg QD continuous dosing for 6 week (42 days) cycles. Sunitinib: 50 mg QD in 6 week (42 days) cycles with 4 weeks continuous dosing followed by 2 week break. Dose modifications are allowed per approved package insert or institutional guidelines. Pharmacokinetic (PK)-guided dosing is not allowed. Every effort should be made to continue patients on the starting sunitinib dose regimen throughout the first cycle, unless toxicity mandates dose modification.

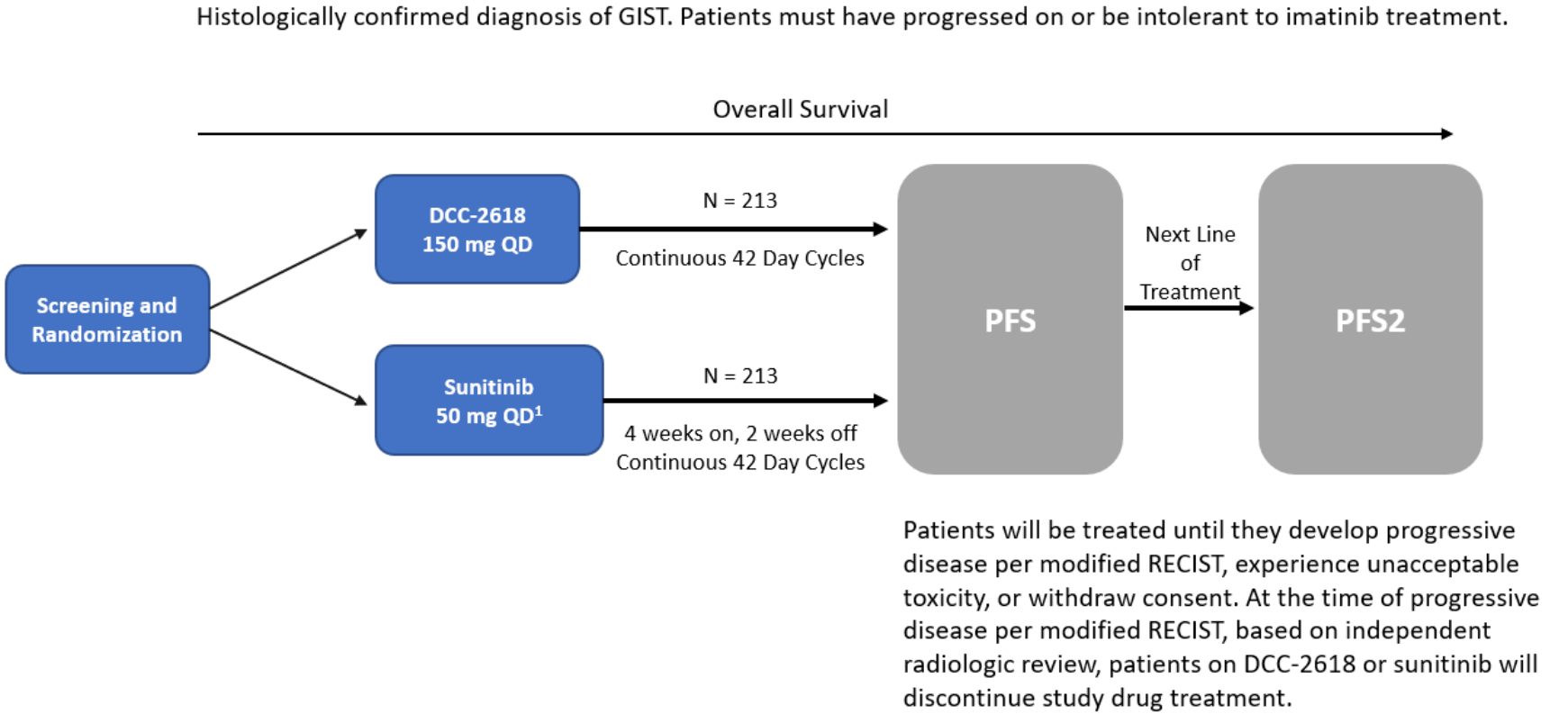
Route of Administration:	Oral
Study Endpoints:	Primary Endpoint: • PFS of DCC-2618 based on independent radiologic review using mRECIST criteria: mRECIST criteria includes: • No lymph nodes chosen as target lesions; enlarged lymph nodes followed as non-target lesions; • No bone lesions chosen as target 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 (e.g. 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 Endpoints: Efficacy: • ORR (confirmed complete response [CR] + confirmed partial response [PR]) based on independent radiologic review using mRECIST criteria • OS The primary and secondary endpoints will be analyzed for both the KIT Exon 11 (Exon 11 ITT) and the All Patients (AP ITT) population. Other Secondary Endpoints: • QOL as measured by using EORTC QLQ-C30, DLQI, and the GP5 questions from FACT-G • TTP based on independent radiologic review • Disease control rate (DCR; CR + PR + stable disease [SD]) at 6, 9, and 12 months, based on independent radiologic review • PFS based on Investigator assessment • Efficacy using Choi criteria based on independent radiologic review Safety: • Treatment-emergent adverse events (TEAEs), adverse events of special interest (AESIs), serious adverse events (SAEs), 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 exposure with efficacy/safety • Population-based PK parameters Exploratory Endpoints: • QOL as measured by EQ-5D-5L, and the memory and concentration items from the PRO-CTCAE library • PFS2: PFS on next line of therapy based on local assessments • Subgroup analyses for efficacy and other endpoints may be explored as data becomes available o Biomarkers and Pharmacodynamics (PDs): ▪ Determine the potential innate and acquired resistance mechanisms to DCC-2618 in GIST. ▪ Assess KIT/PDGFRA mutations and mutant allele frequency at baseline and the treatment effect of DCC-2618 on KIT/PDGFRA mutant allele frequency. o Evaluate the association of anti-tumor activity/safety of DCC-2618 with the following: ▪ baseline KIT/PDFGRA mutation status ▪ expression of KIT protein in tumor ▪ expression or polymorphic variation in drug metabolic and/or drug transporter genes • Changes over time in healthcare utilization
Statistical Considerations:	Randomization: 426 patients will be randomized in 1:1 ratio to DCC-2618 and sunitinib treatment arms. KIT/PDGFRA WT GIST (wild-type KIT and wild-type PDGFRA regardless of the mutational status of any other gene) will be limited to a maximum of up to 10% of the total patient population. Randomization into treatment groups will be stratified by: • Mutational status: KIT exon 9 mutation; KIT exon 11 mutation; KIT/PDGFRA WT; or other KIT (absence of exon 9 or 11)/PDGFRA mutations Note: if a patient has a KIT exon 11 mutation, along with mutation(s) 1) in KIT exon 9 and/or PDGFRA, the patient will be randomized as having a KIT exon 11 mutation, unless the mutation allele frequency (MAF) data is available then the mutation with the higher MAF will be used to categorize the patient for the purposes of randomization; 2) in KIT other exon, the patient will be randomized as having a KIT exon 11 mutation. • Intolerance to imatinib (Yes or No) The KIT Exon 11 Intent-to-Treat (Ex11 ITT) Population is defined as all patients who are designated as having a mutation in KIT Exon 11 at the

	time of randomization. Patients in this population will be analyzed according to the treatment they were scheduled to receive. The All Patients ITT (AP ITT) population is defined as all patients who are randomized. Patients in this population will be analyzed according to the treatment they were scheduled to receive. The primary endpoint PFS and the secondary endpoints will be analyzed in both Ex11 ITT and AP ITT populations. The analysis of PFS in AP ITT will be stratified by the randomization stratification factors (mutation status [KIT exon 9 vs. KIT exon 11 vs. KIT/PDGFRA WT vs. other KIT {absence of KIT exon 9 or 11}/PDGFRA] and intolerance to imatinib [yes vs. no]). Analysis for PFS in Ex11 ITT will be stratified by intolerance to imatinib [yes vs. no]. The p-value will be from a 2-sided stratified Log-rank test at 0.05 significance level for evaluation of treatment difference. Point estimate of hazard ratio will be obtained from a Cox regression model with treatment and the randomization stratification factors as fixed factors and the associated 95% CI will be obtained using the Wald method. Median progression free survival time (mPFS) with 95% confidence interval will also be presented by treatment using KM methodology. The Safety Population is defined as all patients who are randomized and receive at least one dose of study drug. The Safety population will be used for all safety analysis and treatment assignment and will be based on the actual initial study treatment received. The safety parameters include AE, vital signs, laboratory results, LVEF and ECG results. The sample size selection of 426 patients (n=213 DCC-2618, n=213 sunitinib) was based on considerations for powering of the primary endpoint, secondary endpoints, detection of rare safety events and overall exposure to DCC-2618. Under the assumptions that mPFS is 9 months for DCC-2618 and 6 months for sunitinib, the HR is about 0.667 for the AP PFS (sunitinib vs DCC-2618). A total of 262 events will be required to achieve a statistical power of 90% to test the hypothesis of no difference between DCC-2618 and sunitinib in the AP population. Accrual of 426 patients (213 in DCC-2618 and 213 in sunitinib) within 21 months is expected to have 262 PFS events occurred after additional 8 months of follow up. This has accounted for 20% of dropout rate (discontinuation without progressive disease per IRR or death). It is further assumed that the mPFS is 9 months for Ex11 patients in DCC-2618 and 5 months for Ex11 patients in sunitinib, the HR is 0.556 for the Ex11 PFS. It is planned to perform the final analysis on both Ex11 and AP populations at the same time. The final analysis is planned to occur when at least 151 PFS events in Ex11 population and approximately 262 PFS events in AP population have occurred. The 151 PFS events in Ex11 population have at least 95% power to test the hypothesis of no difference between DCC-2618 and sunitinib in KIT Ex11 population.

	All the analysis details will be specified in the protocol and the statistical analysis plan (SAP).
Independent Data Monitoring Committee:	An independent data monitoring committee (IDMC) will monitor the safety and efficacy data from this study on a periodic basis to help ensure the ongoing safety of study patients.
Duration of Study:	Patients will be treated until they develop progressive disease as per mRECIST, based on independent radiologic review, experience unacceptable toxicity, or withdraw consent. At the time of progressive disease by mRECIST, based on independent radiologic review, patients will discontinue study drug. Patients will be eligible to receive study drug for up to 2 years. [redacted] The study will end following the last patient last visit.

Figure 1: Study Schema



[1]Sunitinib dose modifications are allowed per approved package insert or institutional guidelines. Every effort should be made to continue patients on the initial regimen throughout the first cycle, unless toxicity mandates dose modification. PK-guided dosing is not allowed.

Table 1: Schedule of Assessments

Assessments / Procedure[1]	Screening[2]	Cycle 1			Cycle 2		Cycles ≥3		EOT Visit (within 7 days after last dose)	Safety Follow Up	Overall Survival Follow Up[3] (every 3 months ±1 month)
Cycle Day	**-28 to -1**	**1 (Baseline)**	**15 (±1 day)**	**29 (±1 day)**	**1 (±3 days)**	**29 (±3 days)**	**1 (±3 days)**	**29 (±3 days)**		**30 Days Post Last Dose (+5 days)**	
Site Visit	X	X	X	X	X	X	X		X		
Remote Questionnaire Completion[15]								X[15]			
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		X		
Randomization[6]		X									
Clinical Laboratory Tests											
Hematology	X	X	X	X	X	X	X		X		
Serum Chemistries	X	X	X	X	X	X	X		X		
Coagulation[7]	X	X	X[7]	X	X	X	X		X		
Urinalysis	X	X			X		X[8]		X		
TSH, Total T3 and Total T4	X	X					X[9]		X		
Physical Examination	X	Examinations will be driven by clinical findings and/or patient complaints									
ECOG PS[10]	X	X	X	X	X	X	X		X		
Vital Signs and weight[11]	X	X	X	X	X	X	X		X		
Height	X										
12-lead ECG[12]	X	X			X		X		X		
Echocardiogram/MUGA[13]	X						X[13]		X		
Dermatologic Examination[14]	X						X[14]		X		
Adverse Event Reporting	Continuous from signing informed consent through safety follow up										
Concomitant Medications/Procedures		Continuous from on or after the first dose of study drug through safety follow up									

Assessments / Procedure[1]	Screening[2]	Cycle 1			Cycle 2		Cycles ≥3		EOT Visit (within 7 days after last dose)	Safety Follow Up	Overall Survival Follow Up[3] (every 3 months ±1 month)
Cycle Day	-28 to -1	1 (Baseline)	15 (±1 day)	29 (±1 day)	1 (±3 days)	29 (±3 days)	1 (±3 days)	29 (±3 days)		30 Days Post Last Dose (+5 days)	
EORTC QLQ-C30[15]	X	X	X	X	X	X	X	X	X		
EQ-5D-5L[15]		X	X	X	X	X	X	X	X		
Healthcare Utilization		X			X		X		X		
PRO-CTCAE Questions 46 and 47[15]		X	X	X	X	X	X	X	X		
GP5 questions from FACT-G[15]	X	X	X	X	X	X	X	X	X		
DLQI[15]	X	X	X	X	X	X	X	X	X		
Study Drug Administration[16]		X	X	X	X	X	X	X			
Study Drug Dispensation		X			X		X				
PK Sampling[17]		X	X		X		X[17]		X		
Pharmacogenomics[18]		X									
Molecular pathology report with identified KIT/PDGFRA mutation status[19]	X										
[redacted]	[redacted]										
Optional Tumor Biopsy[21]									X		
Radiologic Imaging[22]	X				X		X		X		
[redacted]		[redacted]					[redacted]		[redacted]		

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; DLQI= Dermatology Life Quality Index; MRI=magnetic resonance imaging, MUGA=multigated acquisition; PD=pharmacodynamic; PK=pharmacokinetic; PS=performance status

1. All assessments must be performed predose and within the visit specified windows, unless otherwise described. 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.
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 including OS and PFS2 (i.e. next line of therapy, start date of next line of therapy, date of progression on the next line of therapy).
4. Any medication or non-drug therapy taken, or procedure performed within 30 days prior to screening and before the first dose of study drug.
5. A serum pregnancy test will be performed for females of child-bearing potential by a central laboratory at screening. Urine pregnancy tests will be performed at all subsequent Day 1 visits of each cycle and the EOT visit. Local serum pregnancy test may be performed instead of urine, if it is the standard practice of the site and results are received prior to the patient being dosed in the clinic.
6. Randomization may occur on Day -1. Patients scheduled for Cycle 1 Day 1 on Monday may be randomized on the preceding Friday.

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 by the central laboratory at screening, on Day 1 of Cycles 1, 2, 3 and 4, and the EOT visit and as clinically indicated. If any result is abnormal, a microscopic analysis will be performed by the central laboratory.
9. TSH, Total T3 and Total T4 testing will be performed at screening, on Day 1 of Cycle 1, Day 1 of every odd-numbered cycle (i.e. Cycle 3, Cycle 5, Cycle 7 etc.), and the EOT visit.
10. ECOG PS may be performed pre- or 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.
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 be performed at screening, Cycle 3 Day 1, and Day 1 of every third cycle thereafter (i.e. 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 at screening 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, Day 1 of every third cycle thereafter (i.e. Cycle 6, 9, 12, etc.), the EOT visit and as otherwise clinically indicated. Dermatological 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. Dermatological examinations during the treatment phase may be performed up to 7 days prior to the corresponding study visit or post dose on the day of the study visit. See Section 6.11.6 for further details.
15. The EORTC QLQ-C30, EQ-5D-5L, DLQI, GP5 question from FACT-G, and PRO-CTCAE Questions 46 and 47 must be performed before the patient is evaluated by 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 is not evaluated by the Investigator or designee, the questionnaires do not need to be completed on that day. The GP5 question from FACT-G will be completed first followed by EORTC-QLQ-C30, DLQI, EQ-5D-5L and PRO-CTCAE Questions 46 and 47. The questionnaires will be collected via an electronic patient reported outcome system. Patients will complete all questionnaires at home on Day 29 of Cycle 3 and beyond via the electronic patient report outcome system. Patient-entered data will not be modified by the Investigator or site staff, ePRO vendor, CRO or Sponsor.
16. On days of study visits, patients will be informed to take the study drug at the study site after predose assessments are completed. See Section 5.3 for dosing and administration details.
17. For DCC-2618 patients only, PK sampling will be performed at the following time points: Cycle 1 Day 1 pre-dose and 6 hours after dosing, Cycle 1 Day 15 pre-dose, and 2 and 6 hours after dosing, pre-dose at Day 1 of Cycles 2, 3 and Day 1 of every other cycle thereafter (e.g. Cycle 5, 7, 9, etc.), and at the EOT Visit. All pre-dose 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 onset of a new, suspected, treatment-related adverse event when requested by the Sponsor.
18. **South Korea Only:** Pharmacogenomics samples will not be collected.
19. Molecular pathology report with mutational status of KIT/PDGFRA must be available. Mutation status must be identified using a tissue based PCR/sequencing assay. Molecular pathology report with mutation status of KIT/PDGFRA must be provided to the Sponsor for review prior to randomization. If the molecular pathology report is not available or insufficient, an archival tumor tissue sample or fresh biopsy is required for mutation status confirmation at the central laboratory prior to randomization. Specific instructions will be provided in the Study Reference Manual.

[redacted]

21. All Patients (optional): Additional tumor tissue samples may be collected at the EOT visit and/or 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.
22. 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. CT scans of the pelvis, abdomen, and chest will be performed at screening. Subsequently, CT scans of the pelvis and abdomen will be performed at Days 1 of Cycles 2-7, and Day 1 of every odd-numbered cycle thereafter (e.g. Cycles 9, 11, 13 etc.) and EOT visit. A scan at the EOT visit is not required if disease progression was previously confirmed by independent radiologic review or if less than 28 days have passed since the last scan was performed. 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. Following Cycle 7 Day 1, any initial indication of a partial or complete response based on investigator assessment must be confirmed ≥ 4 weeks following initial response. 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 or at the Investigator's discretion based on the best interest of the patient after discussion with the Sponsor. Additionally, for patients whose local regulatory authority and/or ethics committee has not approved use of CT scans, MRIs may be used. For each patient, the same assessment technique must be used throughout their participation on study unless there is a safety risk as determined by the Investigator. Ultrasound scanning is not an acceptable substitute for CT scanning.
    Validation of No Disease Progression: If the independent radiologic reviewer validates that there is no disease progression per modified RECIST, the patient will continue to receive study drug. If the Investigator determines clinical progression based upon clinical deterioration and wishes to end treatment, a scan must be performed prior to treatment discontinuation. The scan must be submitted to for independent radiologic review. The basis for determination of progression due to clinical deterioration must be documented in the patient's source documents and electronic case report form. If the Investigator's assessment determines disease progression per modified RECIST, the Investigator should wait for confirmation from the independent radiologic review before discontinuing the patient from treatment. If the Investigator wishes to end treatment due to local progression, without confirmation of progression by independent radiographic review, or before the independent read results are available, the Investigator must reach out to the Sponsor Medical Monitor to discuss.

[redacted]

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine transaminase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AP	All Patients
AP-ITT	All Patients Intent to Treat
ASM	Aggressive systemic mastocytosis
AST	Aspartate transaminase
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
CPK	Creatine phosphokinase
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CYP	Cytochrome P450
DCR	Disease control rate
DLQI	Dermatologic life quality index
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

Abbreviation	Definition
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
FACIT	Functional assessment of chronic illness therapy
FACT-G	Functional assessment of cancer therapy - general
FDA	Food and Drug Administration
FFPE	Formalin-Fixed Paraffin-Embedded
FSH	Follicle stimulating hormone
fu	Fraction unbound
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
IRR	Independent radiologic review
IRT	Interactive Response Technology
ITT	Intent to Treat
IV	Intravenous
KM	Kaplan-Meier
LHRH	Luteinizing hormone releasing hormone
LVEF	Left ventricular ejection fraction
MDR1	Multidrug resistance protein 1
MedDRA	Medical Dictionary for Regulatory Activities
mPFS	Modified progression free survival
mRECIST	Modified RECIST criteria

Abbreviation	Definition
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multigated acquisition
NADPH	Nicotinamide adenine dinucleotide phosphate
NCI	National Cancer Institute
NOAEL	No observed adverse effect level
OAT	Organic anion transporter
OCT	Organic cation transporter
ORR	Objective response rate
OS	Overall survival
PD	Pharmacodynamic(s)
PET	Positron emission tomography
PFS	Progression-free survival
PFS2	Progression-free survival 2
PK	Pharmacokinetic(s)
PP	Per protocol
PR	Partial response
PRO	Patient reported outcomes
PS	Performance status
PT	Prothrombin time
PTT	Partial thromboplastin 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
SJS	Stevens Johnson syndrome
SM	Systemic mastocytosis
SOC	System organ class

Abbreviation	Definition
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
ULN	Upper limit of normal
WT	Wild type

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1. INTRODUCTION AND RATIONALE

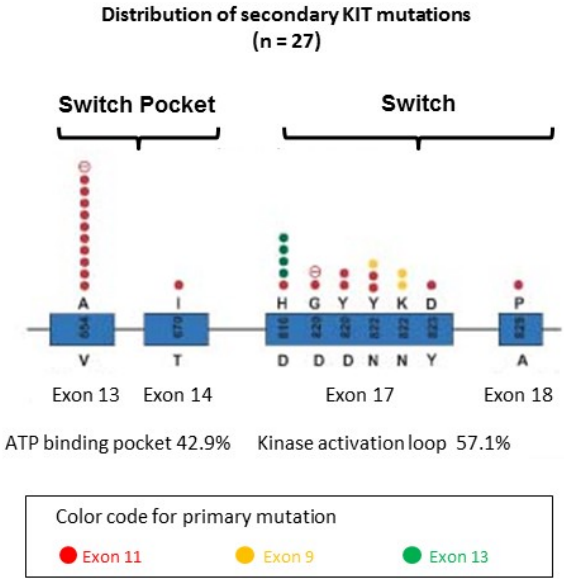
1.1. Introduction

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 (1, 2, 3, 4, 5). In addition, aberrant wild type KIT and/or PDGFRA overexpression is found in GIST, melanoma, AML, gliomas and neuroendocrine tumors (6, 7, 8, 9).

Most GISTs are driven by activating mutations in KIT (~80%) or the related PDGFRA (~10%) receptor tyrosine kinases (11, 36). 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 (10, 11). 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 (12). Other diseases that have primary mutations in the KIT (or PDGFRA) activation loop include SM, AML, and PDGFRA-driven GIST (6, 13, 14).

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 (15). 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% (16). 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 (17). Progression is largely due to secondary mutations in the KIT kinase domain that cause resistance to imatinib (11). 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 (17, 18).

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 (14, 17). 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 (17). 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 (11). 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 (11).

The complex heterogeneity of KIT mutations within individual patients is a major cause of resistance to therapy (11). 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. In the second line setting, sunitinib inhibits secondary resistance mutations in exons 13 and 14 but does not inhibit secondary resistance mutations in exons 17 and 18 (the activation switch region of KIT). 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.

GISTs represent the most common form of sarcoma, a relatively rare subset of cancers arising from mesenchymal cells in the body (19). Adult GIST occurs with an incidence rate of ~3,000-6,000 new cases per year in the US (20, 21, 22), generally presents around age 50-70, and occurs in men and women at similar rates (23). 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 (24). For metastatic or unresectable GIST, which is present in about half of patients at diagnosis, radiotherapy and traditional chemotherapy are not effective (19, 24). The era of targeted cancer therapies has ushered in several new effective treatments for metastatic and recurrent GIST, though CRs are rarely achieved (19). Resistance to therapy occurs in a large majority of patients within a few months to years depending on treatment (20), similar to that observed in other cancers successfully treated with targeted therapies.

1.3. DCC-2618

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 primary initiating mutations of PDGFRA, including KIT primary initiating 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 initiating mutations in exon 18 D842V in the conformation-controlling switch region and in exon 12 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

[redacted]

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. DCC-2618 also inhibited tumor growth in the HMC1.2 (dual exon 11 V560D and exon 17 D816V mutations) mastocytosis xenograft model and exhibited potent inhibition in the PDGFRA amplified H1703 lung cancer xenograft model.

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 postdose and ~40% inhibition at 12-hours postdose. 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. 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.

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1.3.2. Clinical Experience

There are 2 ongoing clinical studies with DCC-2618. A Phase 3 study, DCC-2618-03-001 (invictus), was initiated in January 2018 and is a global, multicenter, double-blind,

placebo-controlled study in patients with advanced GIST who have received at least 3 prior lines of therapy.

The other ongoing study is a Phase 1 Clinical Study, DCC-2618-01-001, which was initiated in November 2015. 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, daily doses of 20 mg to 200 mg BID and 100 to 250 mg QD were given in 28 day cycles. DCC-2618 up to 400mg a day did not result in a dose limiting toxicity (DLT) or maximum tolerated dose (MTD) dose level, and 150 mg QD was selected as the recommended phase 2 dose (RP2D) based on PK, PD, efficacy and safety observed across the dose escalation cohorts. The Expansion Phase is currently enrolling 6 cohorts (3 of these are GIST) and patients in these cohorts are receiving the RP2D of 150 mg QD of DCC-2618. Tumor assessments are every 2 months, per local assessment. Major eligibility criteria include advanced refractory cancers (KIT/PDGFRA mutated) with a focus on GIST, Eastern Cooperative Oncology Group (ECOG) 0-2, and adequate end organ function. Prior treatment with KIT/PDGFRA inhibitors is allowed. More than 100 GIST patients have received the RP2D across dose escalation and expansion in the Phase 1 Clinical Study.

1.3.2.1. Clinical Safety

This section presents clinical safety data for patients that have been enrolled in the Phase 1 Clinical Study of DCC-2618 (DCC-2618-01-001) as of April 18, 2018. Since Study DCC-2618-01-001 is ongoing, some of the clinical data may not be source verified or validated and are therefore subject to change. Please refer to the current version of the IB for additional information.

As of April 18, 2018, 194 patients were treated with DCC-2618, and of those, 100 are still ongoing in the study. Of the 194 patients, 38 patients had non-GIST cancers, and 156 patients had a diagnosis of advanced GIST. The safety data of GIST patients treated at the RP2D/Phase 3 dose of 150mg QD (N=114), is presented in Table 3 below (treatment emergent adverse events [TEAEs] in ≥ 10% GIST patients treated at 150 mg QD). Overall DCC-2618 has been well-tolerated, with very few treatment-related severe adverse events (SAEs) and Grade 3/4 events.

As depicted in Table 3, of the 114 patients with advanced GIST treated at 150 mg QD, 21 patients (18.4%) have had a lipase elevation. Eleven of these were Grade 3-4. Similarly, out of 155 GIST patients in the overall Phase 1 study safety population, 33 (21.3%) of patients had a lipase elevation, 17 with G3-4 (11%). Of all 194 patients treated with DCC-2618 in Phase 1, only two patients have presented with elevated lipase and concomitant signs or symptoms of pancreatitis (abdominal pain, nausea and/or vomiting). Computed tomography (CT) imaging of pancreas was normal in one patient, and slightly thickened/inflamed in the other. Both patients had DCC-2618 interrupted, then shortly after restarted (one patient at a reduced dose), with no recurrent signs or symptoms of pancreatitis. Based on our safety data and experience in 194 patients treated with DCC-2618, the Sponsor does not recommend dose interruption with asymptomatic Grade 3 or 4 elevations of lipase. Continuation of dosing with monitoring for signs or symptoms of pancreatitis is recommended as described in Table 10. Patients are eligible for all current DCC-2618 studies with asymptomatic increases in lipase of ≤ Grade 3, as isolated elevations of serum pancreatic enzymes can be seen with other tyrosine kinase inhibitors.

Not captured in Table 3, is a Grade 3 (severe) SAE of Stevens-Johnson syndrome (SJS)/hypersensitivity reaction. The event was reported as SJS in a 38-year-old Asian female 10 days following the initiation of ripretinib in the Phase I (FIH) study. After a positive re-challenge

at a reduced dose, the study treatment was permanently discontinued due to the event and the event resolved on Day 51 of the study. A Grade 3 SJS corresponds to skin sloughing covering <10% of body surface area. It was considered related to DCC-2618. If a patient experiences SJS/hypersensitivity reaction while being treated with DCC-2618, DCC-2618 must be permanently discontinued.

Table 3: Summary of Treatment Emergent Adverse Events (TEAE) that Occurred in ≥ 10% GIST Patients @ 150 mg QD (n=114)

	Subjects n=114 (%)				
System Organ Class	All	1	2	3	4
Alopecia	48 (42.1)	34 (29.8)	14 (12.3)		
Fatigue	45 (39.5)	32 (28.1)	13 (11.4)		
Myalgia	41 (36.0)	35 (30.7)	6 (5.3)		
Constipation	35 (30.7)	27 (23.7)	8 (7.0)		
Hand-Foot-Syndrome	30 (26.3)	25 (21.9)	4 (3.5)	1 (0.9)	
Rash	26 (22.8)	25 (21.9)	1 (0.9)		
Nausea	25 (21.9)	22 (19.3)	3 (2.6)		
Decreased appetite	22 (19.3)	15 (13.2)	6 (5.3)	1 (0.9)	
Lipase increased	21 (18.4)	7 (6.2)	3 (2.6)	9 (7.9)	2 (1.8)
Diarrhoea	19 (16.7)	15 (13.2)	2 (1.8)	2 (1.8)	
Abdominal pain	17 (14.9)	11 (9.6)	4 (3.5)	2 (1.8)	
Weight decreased	17 (14.9)	14 (12.3)	3 (2.6)		
Arthralgia	16 (14.0)	15 (13.2)	1 (0.9)		
Hypertension	15 (13.2)	3 (2.6)	9 (7.9)	3 (2.6)	
Headache	14 (12.3)	13 (11.4)	1 (0.9)		
Vomiting	14 (12.3)	9 (7.9)	5 (4.4)		
Pain in extremity	14 (12.3)	14 (12.3)			
Dyspnoea	13 (11.4)	9 (7.9)	3 (2.6)	1 (0.9)	
Muscle spasms	13 (11.4)	11(9.6)	2 (1.8)		
Anaemia	12 (10.5)	5 (4.4)	3 (2.6)	4 (3.5)	
Dry skin	12(10.5)	11 (9.6)	1 (0.9)		

1.3.2.1.1. Deaths

As of April 18, 2018, 19 patients were discontinued from the study due to death. Seven of these patients had non-GIST cancer, and 12 GIST. None of the deaths were considered related to study drug.

1.3.2.1.2. Adverse Events of Special Interest

As of 18 April 2018, adverse events of special interest (AESIs) included squamous cell carcinoma (SCC), actinic keratosis, and keratoacanthoma. These events are of special interest because it is unclear if these events are related to DCC-2618. Early in the phase 1 study, DCC-2618-01-001, patients did not receive a baseline dermatologic assessment and had confounding factors that may have contributed to the occurrence of these events. Patients now receive baseline dermatologic assessments for all DCC-2618 studies, and during this study will also have scheduled dermatologic exams.

1.3.2.2. Clinical Pharmacokinetics and Pharmacodynamic Markers

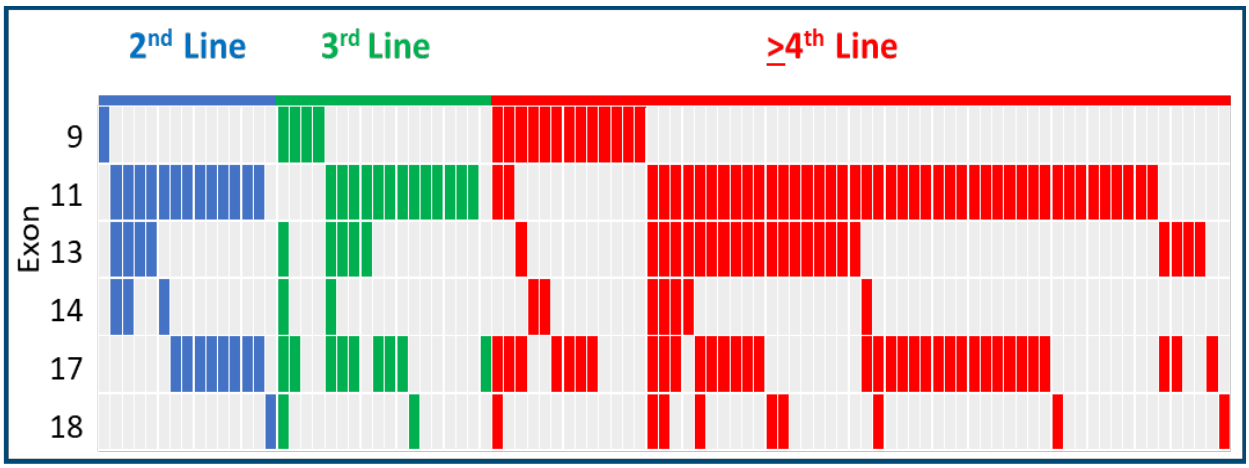
Nonclinical studies had identified DP-5439 as an active metabolite of DCC-2618 with similar activity profile to its parent compound.

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 1.5.2 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 DNA in patients with heavily pretreated GIST. Overall, a high total plasma concentration, determined as $C_{EMEX,}$ was observed exceeding 5 am (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 during the Phase 1 study for GIST patients at baseline, every 2 cycles, while a patient was on study, and at the end of study (Figure 3). Mutations were detected and quantitated by Guardant 360 v2.9 or v2.10. Based on preliminary data (cut-off April 18th, 2018), circulating tumor DNA (ctDNA) was detected in the majority of baseline cfDNA. Mutations in KIT gene across exons 9, 11, 13, 14, 17, and 18 were detected in 95/131 patients with KIT-mutant GIST using baseline ctDNA (Figure 3). The PDGFRA exon 18 mutations were detected in only 2 ctDNA samples out of 9 PDGFRA exon 18 mutant patients enrolled (confirmed by archival tissue testing if tissue was available).

Figure 3: KIT Mutations in Baseline ctDNA (n=95) in 131 GIST Patients by Line of Therapy



Each column represents an individual GIST patient. Each filled entry on rows indicates detection of one or more mutations in Exon 9, 11, 13, 14, 17 and 18 of KIT gene. In pts where a KIT exon 9/11 mutation was detected in baseline ctDNA, secondary KIT mutations in exon 13, 14 ,17 and 18 were found across 2nd to ≥4th line pts.

1.3.2.3. Clinical Efficacy

This section presents clinical efficacy data for patients that have been enrolled as of April 18, 2018, in the Phase 1 Study. Since Study DCC-2618-01-001 is ongoing, some of the clinical data may not be source verified or validated and are therefore subject to change. Please refer to the current version of the IB for additional information.

In the Phase 1 study as of April 18, 2018, 25 of the 156 GIST patients have received 1 prior therapy (i.e. 2nd Line GIST patients) and 29 patients have received 2 prior therapies (i.e. 3rd Line

GIST). All efficacy data uses RECIST 1.1 Criteria with data reported as investigator assessment of scans. For patients at ≥ 100 mg QD with RECIST assessments (n=145), the DCR at 3 months for 2nd line patients is 79%, and for 3rd line patients is 82% with an ORR of 24% for 2nd and 3rd line patients. For ≥ 4th line patients dosed ≥ 100 mg QD (N=91), the DCR is 64% with an ORR of 9% (31). The waterfall plot of best response of KIT/PDGFRA 2nd and 3rd line GIST patients dosed at ≥ 100 mg QD is presented in Figure 4. Figure 4 also presents the baseline ctDNA mutation profile in 2nd line patients previously treated with imatinib, and 3rd line patients previously treated with imatinib and sunitinib.

The Spaghetti Plot of 2nd and 3rd line patients at ≥ 100 mg QD is represented in Figure 5, noting that closed circles are patients still on treatment with DCC-2618.

Figure 4: Waterfall Plot of All KIT/PDGFRA 2nd/3rd Line GIST Patients ≥ 100 mg QD (Best Response per RECIST, N = 54)

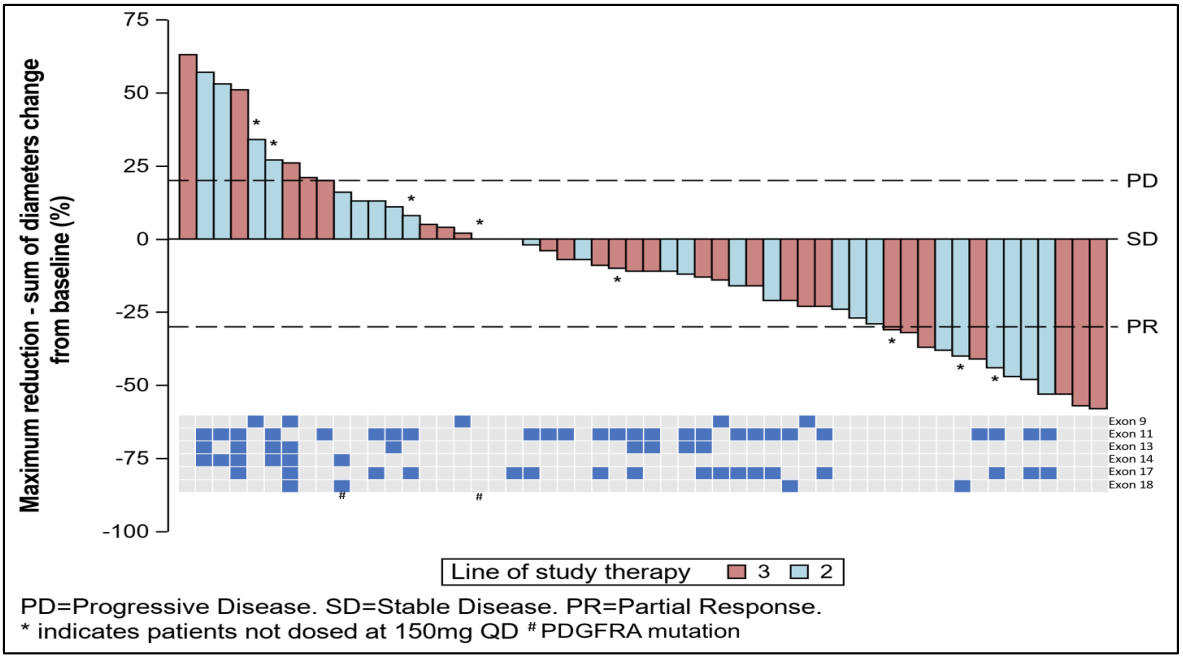
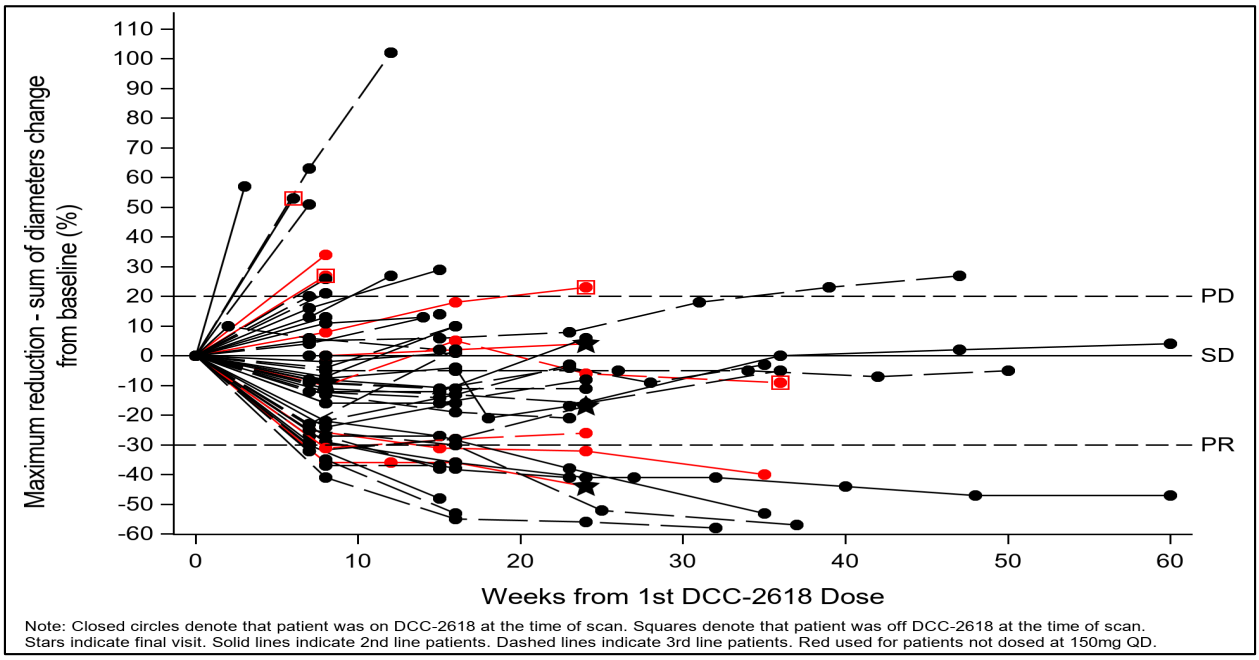


Figure 5: Spaghetti Plots for Disease Control Rate for all 2nd/3rd Line GIST ≥ 100 mg QD Patients (N=54)



1.4. Overview of Sunitinib

Sunitinib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs), some of which are implicated in tumor growth, pathologic angiogenesis, and metastatic progression of cancer. Sunitinib was evaluated for its inhibitory activity against a variety of kinases (> 80 kinases) and was identified as an inhibitor of platelet-derived growth factor receptors (PDGFRα and PDGFRβ), vascular endothelial growth factor receptors (VEGFR1, VEGFR2, and VEGFR3), stem cell factor receptor (KIT), FMS-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor Type 1 (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET). Sunitinib inhibition of the activity of these RTKs has been demonstrated in biochemical and cellular assays, and inhibition of function has been demonstrated in cell proliferation assays. The primary metabolite exhibits similar potency compared to sunitinib in biochemical and cellular assays.

Sunitinib inhibited the phosphorylation of multiple RTKs (PDGFRβ, VEGFR2, KIT) in tumor xenografts expressing RTK targets in vivo and demonstrated inhibition of tumor growth or tumor regression and/or inhibited metastases in some experimental models of cancer. Sunitinib demonstrated the ability to inhibit growth of tumor cells expressing dysregulated target RTKs (PDGFR, RET, or KIT) in vitro and to inhibit PDGFRβ- and VEGFR2-dependent tumor angiogenesis in vivo.

The recommended dose of SUTENT for gastrointestinal stromal tumor (GIST) and advanced renal cell carcinoma is one 50 mg oral dose taken QD, on a schedule of 4 weeks on treatment followed by 2 weeks off (Schedule 4/2). SUTENT may be taken with or without food.

Study NCT#00075218 was a 2-arm, international, randomized, double-blind, placebo-controlled trial of SUTENT in patients with GIST who had disease progression during prior imatinib mesylate (imatinib) treatment or who were intolerant of imatinib. The objective was to compare

time to tumor progression (TTP) in patients receiving SUTENT plus best supportive care versus patients receiving placebo plus best supportive care. Other objectives included PFS, ORR, and overall survival (OS). Patients were randomized (2:1) to receive either 50 mg SUTENT or placebo orally, QD, on Schedule 4/2 until disease progression or withdrawal from the study for another reason. Treatment was unblinded at the time of disease progression. Patients randomized to placebo were then offered crossover to open-label SUTENT and patients randomized to SUTENT were permitted to continue treatment per investigator judgment. In the double-blinded treatment phase, median TTP was 27.3 weeks in the SUTENT group and 6.4 weeks in the placebo group. Median PFS was 24.1 weeks in the SUTENT group and 6. 0 weeks in the placebo group.

1.5. Rationale

1.5.1. Study Rationale

GISTs are predominantly driven by activating mutations in KIT (~80%) or the related PDGFRA (~10%) receptor tyrosine kinases (11, 36). In GIST patients at presentation, mutations in the KIT gene are usually found in exon 9 or 11. Imatinib as first-line therapy is usually not curative in unresectable and/or metastatic disease with CRs seen in ~5% of patients and an ORR of 68% (16). 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 (17). Progression is largely due to secondary mutations in the KIT kinase domain that cause resistance to imatinib (11). Although imatinib is effective against exon11 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 (17, 18).

Sunitinib was approved in 2006 in the US 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 (14, 17). Additionally, sunitinib shows activity against the secondary KIT exon 13 and 14 mutations, but only half the patients show benefit and median PFS is 5.5 months (17). Sunitinib is not effective against KIT exon 17/18 secondary mutations, and not effective against PDGFRA exon 18 activation loop mutations.

DCC-2618 is an orally administered inhibitor of KIT and PDGFRA kinases. DCC-2618 comprehensively and potently inhibits a broad range of primary and secondary mutants of KIT and PDGFRA kinases, including KIT primary initiating mutations in exons 9 and 11 and secondary mutations in exons 13 and 14 of the KIT Switch Pocket region and in exons 17 and 18 of the activation loop conformation controlling Switch; and for PDGFRA the primary exon 18 mutation D842V in the conformation controlling Switch and exon 14 mutations in the PDGFRA Switch Pocket. DCC-2618 also inhibits the non-mutated, (native) wild-type KIT. DCC-2618 exhibits this broad profile of wild-type (native) and mutant KIT/PDGFRA inhibition by binding as an advanced Type II kinase inhibitor that penetrates the embedded KIT/PDGFRA Switch Pocket. DCC-2618 has the potential to provide benefit to patients with all primary mutations, including those not responding to imatinib inhibition, and the broad spectrum of resistance mutations. In the absence of KIT/PDGFRA mutation (WT GIST), the KIT protein is known to be strongly activated in GIST. In imatinib-resistant GISTs, KIT also continues to be expressed strongly (29, 30). These findings indicate that KIT plays an essential role in the pathogenesis of GIST.

DCC-2618 has shown encouraging preliminary clinical activity in patients with advanced GIST in the phase 1 study DCC-2618-01-001. Patients treated at ≥ 100 mg QD had a DCR at 3 months of 79% in 2nd line (N=25), 82% in 3rd line (N=29) and 64% in ≥ 4th line (N=91) of therapy. ORR was 24% in 2nd and 3rd line GIST patients and 9% in ≥ 4th line. The distribution of resistance mutations in KIT across exons 13, 14, 17 and 18 or a combination thereof was found to be similar in 2nd, 3rd and 4th line patients in the Phase 1 study (31), supporting the need of broad mutational coverage in all post-imatinib lines of therapy.

Based on the broad mutational coverage of DCC-2618 in primary and secondary KIT and PDGFRA mutants in KIT exons 9, 11, 13, 14, 17, and 18 and PDGFRA exons 12, 14, and 18, wild type KIT and wild type PDGFRA as well as the manageable toxicity profile and promising efficacy data in the ongoing Phase 1 study, the Sponsor will be initiating this Phase 3 study (intrigue) to study the efficacy of DCC-2618 in patients with GIST previously treated with imatinib. This study is a 2-arm, randomized, open-label, international, multicenter study comparing the efficacy of DCC-2618 to sunitinib in patients with GIST who progressed on or were intolerant of imatinib.

1.5.2. Dose, Regimen, and Treatment Duration Rationale

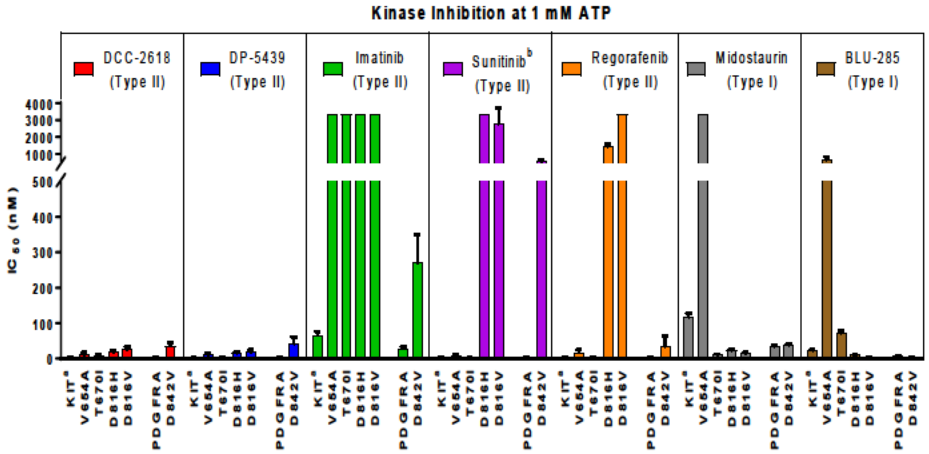
1.5.2.1. Nonclinical Pharmacology and Clinical Pharmacokinetic Analyses to Support Optimal Phase 3 Dose Selection

This section addresses the scientific justification for the selection of a 150 mg QD dose regimen for the Phase 3 studies 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 18 April 2018). Upon completion of the Phase 1 study, clinical PK analysis and evaluation of the exposure-response relationship shall be updated.

1.5.2.1.1. In Vitro Pharmacology

The in vitro pharmacology studies demonstrated DCC-2618 and its active metabolite DP-5439 potently inhibit wild-type and oncogenic KIT and PDGFRA variants with IC_{50} values in the range of 3-36 nM (Figure 6). Data for the currently available KIT inhibitors, imatinib, sunitinib, regorafenib, midostaurin and BLU-285 are shown for reference. At relevant cellular levels of ATP (1 mM), DCC-2618 broadly inhibits KIT mutants in exons 11, 13, 14, and 17, and a PDGFRA exon 18 mutant. Other Type II inhibitors do not block exon 17 mutants such as D816V KIT, whereas Type I inhibitors have weaker activity for exon 13/14 mutants.

Figure 6: DCC-2618 Inhibition of PDGFRA and KIT Mutants



Mutation	Exon
KIT V654A	13
KIT T670I	14
KIT D816H	17
KIT D816V	17
PDGFRA D842V	18

[redacted]

1.5.2.1.2. In Vivo Pharmacology

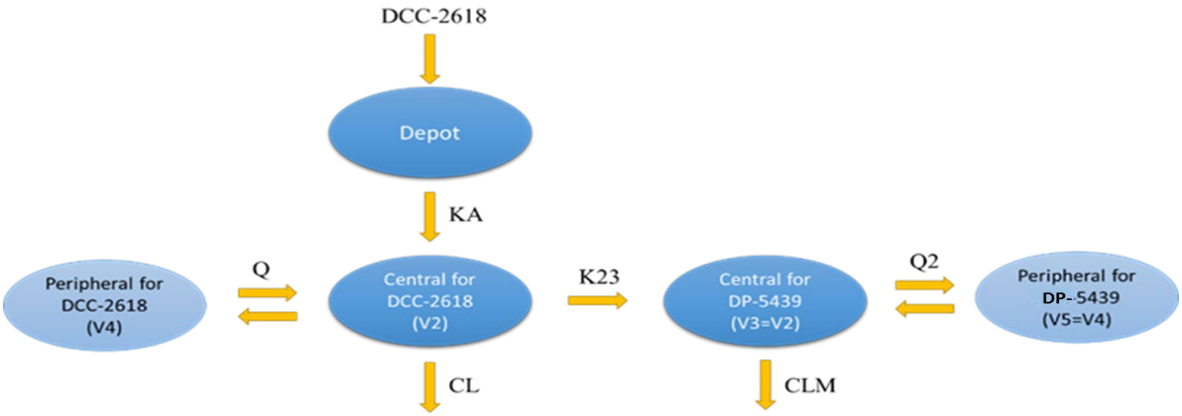
In an exon 11 mutant KIT GIST T1 cell line xenograft mouse model, KIT signaling was suppressed by 69-88% out to 8 hours after administration of a single oral dose of 50 mg/kg DCC-2618 and sustained at ~40% inhibition at 12 hours post-dose. After oral, BID dosing in the GIST T1 xenograft model, DCC-2618 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. In the HMC1.2 mastocytosis xenograft model harboring dual exon 11 V560G and exon 17 D816V mutations, DCC-2618 oral administration at 25 and 100 mg/kg daily doses led to dose related decreases in tumor burden. In the PDGFRA amplified H1703 lung xenograft model, 25mg/kg daily dose led to near complete inhibition of tumor growth, while 100 mg/kg daily dose led to tumor regression.

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.

1.5.2.1.3. 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 7. 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 7: 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 is shown in Table 4.

Table 4: 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)	$AUC_{0\text{-}24hr}$ (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

Dosing Interval	Dose	Analyte	C_{trough} (ng/mL)	C_{max} (ng/mL)	AUC_{0-24hr} (ng·h/mL)
QD	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
	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.

1.5.2.1.4. 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 unlikely 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.

2. STUDY OBJECTIVES

2.1. Primary Objective

- 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 previously received first-line therapy with imatinib

2.2. Secondary Objectives

2.2.1. Key Secondary Objectives

- To assess objective response rate (ORR) by independent radiologic review using mRECIST criteria
- To assess Overall Survival (OS)

2.2.2. Other Secondary Objectives

- To assess the quality-of-life (QOL) during treatment as measured by:
  - EORTC QLQ-C30
  - Dermatology Life Quality Index (DLQI)
  - GP5 question from the FACT-G (burden of side-effects)
- To assess Time to Tumor Progression (TTP) by independent radiologic review
- To assess efficacy parameters, including disease control rate (DCR), PFS based on Investigator assessment, and efficacy based on Choi criteria by independent radiologic review
- To assess the PK/PD relationship of DCC-2618
- To compare the safety profile of DCC-2618 to the safety profile of sunitinib

2.3. Exploratory Objectives

- To assess QOL during treatment as measured by:
  - Memory and concentration items from the PRO-CTCAE library
  - EQ-5D-5L
- To assess Progression Free Survival on next line therapy (PFS2) based on local assessments
- To evaluate potential biomarkers in blood or tumor tissue which might predict response to DCC-2618
  - To understand potential resistance mechanisms to DCC-2618 in GIST
  - To characterize KIT and PDGFRA mutations at baseline and DCC-2618-driven longitudinal mutant allele frequency changes in plasma.
- To assess healthcare utilization

3. STUDY DESIGN

3.1. Overview of Study Design

This is a 2-arm, randomized, open-label, international, multicenter study comparing the efficacy of DCC-2618 to sunitinib in GIST patients who progressed on or were intolerant to first-line anticancer treatment with imatinib.

Approximately 426 patients will be randomized in a 1:1 ratio to DCC-2618 150 mg QD or sunitinib 50 mg QD, 4 weeks on, 2 weeks off (see Figure 1). Up to 10% of patients randomized may have KIT/PDGFRA WT GIST (wild-type KIT and wild-type PDGFRA regardless of the mutational status of any other gene). Randomization will be stratified by:

- Mutational Status: KIT exon 9 mutation; KIT exon 11 mutation; KIT/PDGFRA WT; or other KIT (absence of exon 9 or 11)/PDGFRA mutations
- Intolerance to imatinib (Yes or No)

The primary endpoint for the study will be evaluated using the mRECIST Version 1.1 – GIST specific (hereafter referred to as "mRECIST") based on independent radiologic review.

Upon disease progression by mRECIST based on independent radiologic review, patients will discontinue their assigned treatment.

NOTE: If the Investigator wishes to end treatment due to local progression based on mRECIST, without confirmation of progression by independent radiographic review, or before the independent read results are available, the Investigator must reach out to the Sponsor Medical Monitor to discuss.

3.2. Number of Patients

Approximately 426 patients (213 randomized to DCC-2618 and 213 randomized to sunitinib) will be randomized in this study at approximately 125 centers globally.

3.3. Duration of Study

Patients will be treated until they develop progressive disease as per mRECIST, experience unacceptable toxicity, or withdraw consent. At the time of progressive disease by mRECIST, based on independent radiologic review, patients will discontinue study drug. Patients will be eligible to receive study drug for up to 2 years. 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. Patients ≥ 18 years of age at the time of informed consent.
2. Histologic diagnosis of GIST and must be able to provide an archival tumor tissue sample, otherwise, a fresh biopsy is required.
3. Molecular pathology report with mutational status of KIT/PDGFRA must be available. Mutation status must be identified by using a tissue-based PCR/sequencing assay. Molecular pathology report with mutation status of KIT/PDGFRA must be provided to the Sponsor for review prior to randomization. If molecular pathology report is not available or insufficient, an archival tumor tissue sample or fresh biopsy is required for mutation status confirmation by the central laboratory prior to randomization.
4. Patients must have progressed on imatinib or have documented intolerance to imatinib. Imatinib treatment must have been discontinued 10 days prior to the first dose of study drug. All prior imatinib treatment will count as one line of therapy (e.g. adjuvant imatinib and dose escalation of imatinib).
5. Eastern Cooperative Oncology Group (ECOG) PS of ≤ 2 at screening.
6. Female patients of childbearing potential must have a negative serum beta-human chorionic gonadotropin (β-hCG) pregnancy test at screening and 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 6.11.9.
8. Patients must have at least 1 measurable lesion according to mRECIST Version 1.1 (non-nodal lesions must be ≥ 1.0 cm in the long axis or ≥ double the slice thickness in the long axis) within 21 days prior to the first dose of study drug.
9. Adequate organ function and bone marrow reserve as indicated by the following central laboratory assessments performed at screening.
    - Absolute neutrophil count (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 (AST) and alanine transaminase (ALT) ≤ 3 x ULN (≤ 5x ULN in the presence of hepatic metastases)
    - Creatinine clearance ≥ 50 mL/min based on Cockcroft Gault estimation
    - Prothrombin time (PT), international normalized ratio (INR), and partial thromboplastin time ≤ 1.5 x ULN. Patients on a stable regimen of anticoagulant therapy for at least one month prior to first dose of study drug 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.

10. Resolution of all toxicities from prior therapy to ≤ Grade 1 (or patient baseline) within 1 week prior to the first dose of study drug (excluding alopecia and ≤ Grade 3 clinically asymptomatic lipase, amylase, and creatine phosphokinase [CPK] laboratory abnormalities).
11. The patient is capable of understanding and complying with the protocol and the patient has signed the informed consent document. Signed informed consent form (ICF) must be obtained before any study-specific procedures are performed and the patient must agree to not participate in any other interventional clinical trial while on treatment in this clinical trial. Participation in a noninterventional study (including observational studies) is permitted.

4.2. Exclusion Criteria

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

1. Treatment with any other line of therapy in addition to imatinib for advanced GIST. Imatinib-containing combination therapy in the first-line setting is not allowed.
2. Patients with a prior or concurrent malignancy whose natural history or treatment have the potential to interfere with the safety or efficacy assessment of this clinical trial are not eligible. For example, patients receiving adjuvant cancer treatment are not eligible if those medications are potentially active against GIST or excluded per protocol.

   NOTE: Patients with a history of breast cancer, requiring continued hormonal treatment (e.g. anti-estrogen or an aromatase inhibitor) may continue treatment. Patients with a history of prostate cancer, requiring continued support with luteinizing hormone-releasing hormone (LHRH) agonists, with or without androgens, may continue treatment.

   NOTE: Patients may not be part of an ongoing or have prior participation in an investigational drug study within 30 days of screening.
3. Patient has known active central nervous system metastases.
4. New York Heart Association class II-IV heart disease, myocardial infarction within 6 months of cycle 1 day 1, active ischemia or any other uncontrolled cardiac condition such as angina pectoris, clinically significant cardiac arrhythmia requiring therapy, uncontrolled hypertension or congestive heart failure.
5. Left ventricular ejection fraction (LVEF) < 50% at screening.
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 (e.g. deep vein thrombosis) or pulmonary arterial events (e.g. pulmonary embolism) within 1 month before the first dose of study drug. Patients on stable anticoagulation therapy for at least one month are eligible.
8. 12-lead ECG demonstrating QT interval corrected (QTc) by Fridericia's formula > 450 ms in males or > 470 ms in females at screening or history of long QT syndrome.

9. Use of strong or moderate inhibitors or inducers of cytochrome P450 (CYP) 3A4, including certain herbal medications (e.g. St. John's Wort) within 14 days or 5 x the half-life (whichever is longer) prior to the first dose of study drug, and consumption of grapefruit or grapefruit juice within 14 days 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/induce CYP3A4 enzymes. See Section 5.12.3.2.
10. 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 US Food and Drug Administration's (FDA) website for inhibitors and substrates (https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm). See Section 5.12.3.2
11. Major surgeries (e.g. abdominal laparotomy) within 4 weeks of the first dose of study drug. All major surgical wounds must be healed and free of infection or dehiscence before the first dose of study drug.
12. 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.
13. Known human immunodeficiency virus or hepatitis C infection only if the patient is taking medications that are excluded per protocol (See Section 5.12.3.2), active hepatitis B, or active hepatitis C infection.
14. If female, the patient is pregnant or lactating.
15. Known allergy or hypersensitivity to any component of the study drug. Patients with a history of Stevens-Johnson syndrome on a prior tyrosine kinase inhibitor (TKI) are excluded.
16. Gastrointestinal abnormalities including but not limited to:
    - inability to take oral medication
    - malabsorption syndromes
    - requirement for intravenous (IV) alimentation
17. Any active bleeding excluding hemorrhoidal or gum bleeding.

5. STUDY DRUG ADMINISTRATION AND MANAGEMENT

Study drug will refer to sunitinib and DCC-2618. In cases where there is a distinction in how they are to be administered and managed, details for each will be specified.

5.1. Sunitinib

5.1.1. Sunitinib Description

Sunitinib will be supplied as printed hard shell capsules containing sunitinib malate equivalent to 12.5 mg of sunitinib together with mannitol, croscarmellose sodium, povidone (K-25) and magnesium stearate as inactive ingredients.

5.2. DCC-2618

5.3. 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 50 mg of sunitinib in repeated 42-day cycles. DCC-2618 will be given continuously and sunitinib will be given continuously for 4 weeks with a 2 week break. Sunitinib dose modifications are allowed per approved package insert or institutional guidelines. Every effort should be made to continue patients receiving sunitinib on a schedule of 4 week on, 2 week off regimen throughout the first cycle, unless toxicity mandates dose modification. PK-guided sunitinib dose escalation is not allowed.

The Investigator or designee must instruct the patient to take DCC-2618 as follows:

- Patients should be instructed to take their assigned dose at the same time each day.
- Patients should take DCC-2618 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 DCC-2618 administration must be recorded for the 3 days prior to PK sample collections and on the days of PK sample collection.

If a patient forgets to take a dose of DCC-2618 at the scheduled time, the patient can take the scheduled dose if taken within 8 hours of the scheduled time that was missed. If more than 8 hours have passed after the scheduled time, then that missed dose must be omitted, and the patients must continue treatment with the next scheduled dose.

For dosing instructions of sunitinib, refer to the approved package insert or institutional guidelines.

On days of planned study visits, patients will be informed to take the study drug at the study site as per Table 1 (schedule of assessments). 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 in the patient's source documents.

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 and the approved package insert or institutional guidelines for sunitinib.

5.4. Study Drug Dose Interruption and Modification

Sunitinib dose interruption and modification will follow guidelines as per the approved package insert or institutional guidelines. PK-guided sunitinib dosing is not allowed. Upon resumption following a dose interruption, the Investigator must continue with the patient's original visit schedule calculated from Cycle 1 Day 1 (i.e. cycle day count is continuous and does not pause with a dose interruption). Clinic visits and assessments should continue during dose interruptions as per Table 1 (schedule of assessments). Dose interruptions of longer than 28 consecutive days will result in the patient being discontinued from the study. If the patient is on 4 weeks on, 2 weeks off cycle, the 28 days is inclusive of the 2 weeks off.

DCC-2618 may be interrupted or modified (i.e. dose reduction) at the discretion of the Investigator at any time due to AE, to accommodate palliative treatment, or for other reasons after consultation with the Sponsor. An interruption must be limited to no more than 28 consecutive days. Upon resumption following a dose interruption, the Investigator must continue with the patient's original visit schedule calculated from Cycle 1 Day 1 (i.e. cycle day count is continuous and does not pause with a dose interruption). Clinic visits and assessments should continue during dose interruptions as per Table 1 (schedule of assessments). Dose interruptions of longer than 28 consecutive days will result in the patient being discontinued from the study.

5.4.1. Study Drug Dose Interruption due to Planned Medical Procedures

Sunitinib should be interrupted for major surgical procedures as per institutional guidelines or the approved package insert.

For DCC-2618, 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: DCC-2618 must be interrupted for 3 days prior to and 3 days after surgery.
- Planned major surgery: DCC-2618 must be interrupted for 5 days prior to and 5 days after surgery.
- Unplanned/emergent surgery: DCC-2618 must be interrupted immediately and restarted as described above for minimally invasive and/or major surgery.

5.4.2. DCC-2618 Interruption and Modification Due to Toxicity

DCC-2618 may be interrupted or reduced as described in Table 5 at the discretion of the Investigator at any time due to AEs and according to the guidelines described in Table 6, Table 7, Table 8, Table 9 and Table 10. Whenever possible, dose reductions should be

prospectively discussed with the Sponsor. If DCC-2618 is interrupted and then DCC-2618 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 OS and PFS2.

Table 5: Dose Reduction Steps for DCC-2618

Starting Dose of DCC-2618	1ST Dose Reduction	2ND Dose Reduction
150 mg QD	100 mg QD	50 mg QD

If the AE returns to Grade 1 or baseline, the patient should 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 (42 days), then DCC-2618 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 6: DCC-2618 Dose Modifications for Left Ventricular Systolic Dysfunction

Toxicity Grade	Management Guideline
Any Grade 3 or 4	Permanently discontinue DCC-2618

Table 7: DCC-2618 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 DCC-2618 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 DCC-2618 at the current dose level Hold DCC-2618 if symptomatic increase by 20 mmHg (diastolic BP) until symptoms resolve and diastolic BP ≤90 mmHg On resuming DCC-2618, 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 DCC-2618 until diastolic BP ≤90 mmHg and/or systolic BP ≤140 mmHg, and symptoms resolve On resuming DCC-2618, continue at the same dose level If BP is not controlled with addition of a new or more intensive therapy, reduce DCC-2618 by 1 dose level If Grade 3 hypertension recurs despite DCC-2618 dose reduction and antihypertensive therapy, reduce the DCC-2618 by 1 additional dose level
Grade 4 **Life-threatening consequences (e.g. malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis)**	Treat BP per institutional guidelines Permanently discontinue DCC-2618

BP=blood pressure

*If BP remains controlled for at least 28 days, DCC-2618 dose re-escalation is permitted at the Investigator's discretion.

Table 8: DCC-2618 Dose Modifications for Dermatologic Toxicities (except Alopecia) and Arthralgia/Myalgia

Toxicity Grade[1]	Dose Modification Guide
Grade 1	Institute support measures and continue DCC-2618 at the current dose
Grade 2	Institute support measures and continue DCC-2618 at the current dose If no improvement within 7 days, then interrupt DCC-2618 • If the event returns to Grade 1 or baseline within 7 days, resume DCC-2618 at the same dose level • If the event returns to Grade 1 or baseline after 7 days, resume DCC-2618 at a reduced dose level If this is a recurrence, after event returns to Grade 1 or baseline, resume DCC-2618 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 (42 days) of dosing, consider re-escalating DCC-2618 by 1 dose level
Grade 3	Institute support measures Interrupt DCC-2618 for at least 7 days or until the event returns to Grade 1 or baseline (maximum 28 days) • Resume DCC-2618 at a reduced dose level If after a dose reduction the event is maintained at Grade 1 or baseline for at least 1 cycle (42 days) of dosing, consider re-escalating DCC-2618 by 1 dose level
Grade 4	Discontinue DCC-2618 unless the event is not considered life-threatening. Patients may continue DCC-2618 with non-life threatening events upon discussion with the Sponsor.
Grade: Any	**Stevens-Johnson Syndrome / Hypersensitivity Reaction:** If a patient experiences Stevens-Johnson syndrome (SJS)/hypersensitivity reaction while being treated with DCC-2618, DCC-2618 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 DCC-2618 is not allowed due to the risk of recurrent SJS/hypersensitivity reaction. Caution for recurrence of SJS with other similar agents (TKIs for GIST) is advised.
[1]The severity of an AE that does not appear in the CTCAE v.5.0 scale must be assessed according to the criteria in Table 12**.**	

Table 9: DCC-2618 Dose Modifications for Isolated Bilirubin Increased

Toxicity Grade	Management Guideline
Grade 2	Interrupt DCC-2618 until toxicity resolves to Grade 1 or baseline (maximum 28 days); resume DCC-2618 at 100 mg.
Grade 3 or 4	Interrupt DCC-2618 until toxicity resolves to Grade 1 or baseline (maximum 28 days); otherwise permanently discontinue DCC-2618. If the event returns to Grade 1 or baseline, resume DCC-2618 at 100 mg. If the reduced dose is tolerated without recurrence of the event for at least 28 days, consider re-escalating DCC-2618. If Grade 3 or higher toxicity recurs, discontinue DCC-2618 permanently.

Table 10: DCC-2618 Dose Modifications for Treatment Related Adverse Events Not Mentioned Above

Toxicity Grade	Management Guideline[1]
Any Grade 3 or 4	Interrupt DCC-2618 dosing until event has resolved to Grade 1 or baseline Once the AE returns to Grade 1 or baseline, reduce DCC-2618 by 1 dose level If a patient tolerates the reduced dose without recurrence of the event for at least 28 days, consider re-escalating the dose of DCC-2618 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 DCC-2618 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 DCC-2618 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 DCC-2618 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 the DCC-2618. If the Investigator assesses that restarting DCC-2618 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.

5.5. 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.

Sutent® (sunitinib malate) 12.5 mg oral capsules will be supplied in its original form in 30 count HDPE bottles and relabeled by the Sponsor.

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.

5.6. Study Drug Storage Conditions

DCC-2618 bottles must be stored tightly closed between 5°C-25°C (41°F-77°F). Keep away from areas of high humidity and sunlight (i.e. near showers in bathrooms) and according to the instructions provided in the Pharmacy Manual. Excursions between 2°C-27°C (35.6°F-80.6°F) are allowed.

Instructions regarding the storage and handling of DCC-2618 after dispensation to patients will be provided to site in the Pharmacy Manual.

Refer to the provided package insert for information on sunitinib storage and handling.

While at the clinical site, 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 or Investigator statement.

5.7. 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.

5.8. 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 study monitor 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.

5.9. 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 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.

5.10. Method of Assigning Patients to Treatment

Patients will be randomized in a 1:1 ratio to DCC-2618 150 mg or sunitinib 50 mg. Up to 10% of randomized patients may have KIT/PDGFRA WT GIST (wild-type KIT and wild-type PDGFRA regardless of the mutational status of any other gene). Randomization will be stratified by:

- Mutational Status: KIT exon 9 mutation; KIT exon 11 mutation; KIT/PDGFRA WT; or other KIT (absence of exon 9 or 11)/PDGFRA mutations
- Intolerance to imatinib (Yes or No)

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

5.11. Blinding and Unblinding

This is an open-label study.

5.12. Prior and Concomitant Treatment and Procedures

5.12.1. Prior Medications and Procedures

Information regarding any medication including vitamin supplements, over-the-counter medications, and oral herbal preparations or non-drug therapy taken, or procedure performed within 30 days prior to signing informed consent 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 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. 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.

5.12.3.1. Permitted Medication

Patients may receive medications for symptomatic relief (e.g. analgesics, laxatives, antiemetics) as long as they are not prohibited by the protocol.

For sunitinib, refer to the approved package insert or institutional guidelines.

5.12.3.2. Prohibited Medications and Substances

Prohibited medications and certain foods are not allowed from screening through the Safety Follow-up Visit. Except for study drug, anticancer therapies active or potentially active against GIST are prohibited during this study.

Prior to randomization, all patients must follow the exclusions listed below:

- Treatment with imatinib within 10 days prior to the first dose of study drug, or any other anticancer medication or line of therapy for advanced GIST.
- Strong or moderate inhibitors or inducers of CYP3A4, including certain herbal medications (e.g. St. John's Wort): discontinue at least 14 days (or 5x 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: must not be consumed at least 14 days prior to first dose of study drug
- Known substrates or inhibitors of BCRP transporters: discontinue at least 14 days or 5x 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 for BCRP.

After randomization and during the study, patients randomized to sunitinib will follow the approved package insert or institutional guidelines for prohibited medications.

The following are prohibited after randomization and during the study for patients randomized to DCC-2618:

- Strong and moderate inducers of CYP3A, including certain herbal medications (e.g. St. John's Wort)

  Please refer to the Indiana University Department of Medicine website (http://medicine.iupui.edu/clinpharm/ddis/main-table/) for guidance on medications that induce CYP3A4 enzymes.

5.12.3.3. Medications to Avoid if possible or Take with Caution

After randomization and during the study for patients randomized to DCC-2618, the following medications should be avoided if possible or taken with caution following discussion with the Sponsor for patients receiving DCC-2618 (sites will be provided with updated information during the study):

- Strong or moderate inhibitors of CYP3A including grapefruit juice

- Known substrates or inhibitors of BCRP transporters and P-glycoprotein 1 (permeability glycoprotein, also known as MDR1). Please refer to the FDA's website for inhibitors http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

- Medications dependent on CYP2C8 for their metabolism. Please refer to the Indiana University Department of Medicine website (http://medicine.iupui.edu/clinpharm/ddis/main-table/) for guidance on these medicines.

Patients taking any of the above listed medications must be closely monitored for any potential drug-drug interactions with DCC-2618.

For sunitinib drug-drug interactions, refer to the approved package insert or institutional guidelines.

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. Patients with PR are permitted resection of remaining tumor, but only after they have been on treatment for 12 months. If the Investigator believes it is in the best interest of the patient, surgical resection or palliative radiotherapy may be performed after discussion with the Sponsor. The patient will 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 who are taking DCC-2618 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 taking DCC-2618 include sunscreen with SPF $\geq$ 30, hypoallergenic moisturizing creams or ointments for dry skin, and gentle skincare with fragrance-free soaps and detergents.

For sunitinib precautions, refer to the approved package insert or institutional guidelines.

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 and dermatologic examination 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). Imaging assessments, echocardiogram/MUGA, and dermatologic examinations 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). 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 30 days (+5 days) after the last dose of study drug to assess AEs; medications, including anticancer treatments; and procedures (see Section 6.11.11 for further details). Patients will be contacted by phone call for OS and PFS2 (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.

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, EuroQol 5 Dimension 5 Level (EQ-5D-5L), DLQI, GP5 question from FACT-G, and the memory and concentration parts of the PRO-CTCAE questionnaires must be performed before the patient is evaluated by 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 is not evaluated by the Investigator or designee, the questionnaires do not need to be completed on that day. The GP5 question from FACT-G will be completed first followed by EORTC-QLQ-C30, DLQI, EQ-5D-5L and the memory and concentration parts of the PRO-CTCAE.

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

6.7. Informed Consent Procedure

Each patient must sign and date a study-specific 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 ICF 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 (e.g. tumor tissue sample only, R0, R1, or R2)
    - Prior imatinib therapy: include dates of treatment, including dose and dosing regimen, reason for treatment (e.g. 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)

Molecular pathology report with mutational status of KIT/PDGFRA must be provided to the Sponsor for review prior to randomization. If molecular pathology report is not available or insufficient, an archival tumor tissue sample or fresh biopsy is required for mutation status confirmation prior to randomization. Specific instructions will be provided in the Study Reference Manual.

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 CT scans of the pelvis, abdomen, and chest according to Table 1 (schedule of assessments). 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. Following Cycle 7 Day 1, an initial indication of a PR or CR based on investigator assessment must be confirmed ≥ 4 weeks following initial response. 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 or per Investigator's discretion based on the best interest of the patient after discussion with the Sponsor. 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 used on a patient at screening must continue to be used for that patient for the duration of their study participation unless there is a safety risk as determined by the Investigator. 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. 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 mRECIST (see Section 9.2.1.1). Response as determined by the Investigator will be recorded in the eCRF. Data from the independent radiologic review (IRR) will be used for the primary endpoint analysis. The IRR will also assess tumor response using Choi criteria, and this will be used for a secondary endpoint. More details on image acquisition guidelines and radiographic assessment will be provided in a separate protocol specific manual.

Confirment of Disease Progression (by IRR): [redacted] A scan is not required at the EOT visit if disease progression was previously confirmed by independent radiologic review.

Confirmation of No Disease Progression (by IRR): If the independent radiologic reviewer confirms that there is no disease progression, the patient will continue to receive study drug.

- If the Investigator determines clinical progression based upon clinical deterioration and wishes to end treatment, a scan must be performed prior to treatment discontinuation. The scan must be submitted to for independent radiologic review. The basis for determination of progression due to clinical deterioration must be documented in the patient's source documents and eCRF. If the Investigator's assessment determines disease progression per mRECIST, the Investigator should wait for confirmation from the independent radiologic review before discontinuing the patient from treatment.
- If the Investigator wishes to end treatment due to local progression based on mRECIST, without confirmation of progression by independent radiographic review, or before the independent read results are available, the Investigator must reach out to the Sponsor Medical Monitor to discuss.

6.10.2. Overall and PFS2 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, including OS and PFS2 (i.e. next line of therapy, start date of next line therapy, and the date of progression on the next line of therapy).

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 QOL in patients with cancer (25). The time required for completion is approximately 12 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/QOL scale.

The patient is asked 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." Two items assess the patient's global health status over the past week using self-reported 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 before dosing at the visits indicated in Table 1 (schedule of assessments). If the EORTC-QLQ-C30 is not available in the patient's native

language, the patient will be exempt from taking the questionnaire. Patient-entered data will not be modified by the Investigator or site staff, ePRO vendor, CRO or Sponsor.

6.10.3.2. Dermatology Life Quality Index

The Dermatology Life Quality Index (DLQI) is a validated questionnaire used to measure the impact of skin symptoms on the QOL of an affected person (32). There are 10 questions, covering the following topics: symptoms, embarrassment, shopping and home care, clothes, social and leisure, sport, work or study, close relationships, sex, and wider treatment consequences. Each question refers to the impact of the skin disease on the patient's life over the previous week. Each question is scored at four levels from "Not at all" (0), through "A little", and "A lot", to "very much"(3), giving a possible summary score range from 0 (meaning no impact of skin disease on QOL to 30 (meaning maximum impact on QOL. A difference of four is considered to be clinically significant in inflammatory skin disease. Validated translations will be provided for sites in non-English speaking countries.

Patients will be asked to complete DLQI in their native language using an ePRO system before dosing at the visits indicated in Table 1 (schedule of assessments). If the DLQI is not available in the patient's native language, the patient will be exempt from taking the questionnaire. Patient-entered data will not be modified by the Investigator or site staff, ePRO vendor, CRO or Sponsor.

6.10.3.3. GP5 Question from FACT-G

The GP5 burden-of-side-effects question, a part of the Functional Assessment of Chronic Illness Therapy (FACIT) Functional Assessment of Cancer Therapy - General (FACT G) questionnaire, is a validated, standardized, patient completed question used extensively in international clinical studies (33). It was developed to assess health related QOL in patients with cancer. The time required for completion is approximately 20 seconds. The question is completed by the patient's selection of one of the following options of "not at all," "a little bit," "somewhat," "quite a bit," and "very much". Validated translations will be provided for sites in non-English speaking countries.

Patients will be asked to complete the GP5 question from FACT G in their native language using an ePRO system before dosing at the visits indicated in Table 1 (schedule of assessments). If the GP5 question from FACT-G is not available in the patient's native language, the patient will be exempt from taking the questionnaire. Patient-entered data will not be modified by the Investigator or site staff, ePRO vendor, CRO or Sponsor.

6.10.3.4. Memory and Concentration Portions of PRO-CTCAE Library

The NCI-PRO-CTCAE measurement system was developed to gather symptomatic AEs by patient self-reporting (34). The NCI-PRO-CTCAE library is comprised of 124 items representing 78 symptomatic AEs. The NCI-PRO-CTCAE items evaluate symptom attributes such as symptom occurrence, frequency, severity, and interference with daily activities, and are intended to be complementary to the items in the NCI's CTCAE. Validated translations will be provided as available for specific non-English speaking countries. If validated translations are not available for the patient, the patient will be exempt from completing this questionnaire.

Patients will be asked to complete questions 46 and 47 of the PRO-CTCAE in their native language, if available, using an ePRO system before dosing at the visits indicated in Table 1 (schedule of assessments). The time to fill out all the questions is less than a minute. Patient-

entered data will not be modified by the Investigator or site staff, ePRO vendor, CRO or Sponsor.

Patients are asked to rate the severity of problems with concentration/memory on a five level Likert scale going from None to Very severe. They are also asked to rate how much those problems interfered with their usual activities on a five-level Likert Scale going from Not at all to Very much.

6.10.3.5. 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 (26). The time required for completion is approximately 2 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 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 in their native language using an ePRO system before dosing at the visits indicated in Table 1 (schedule of assessments). If the EQ-5D-5L is not available in the patient's native language, the patient will be exempt from taking the questionnaire. Patient-entered data will not be modified by the Investigator or site staff, ePRO vendor, CRO or Sponsor.

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

ECOG PS (27) will be assessed according to the schedule of assessments in Table 1 (schedule of assessments). ECOG PS 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 Table 1 (schedule of assessments). 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). 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, QT interval corrected using Bazett's formula (QTcB) ($QTcB = QT/RR^{0.50}$) and QT interval corrected by Fridericia's formula (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 Table 1 (schedule of assessments). 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. 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 Table 1 (schedule of assessments) and as clinically indicated. The examinations must include the entire skin. Any 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. Comparative analysis of all patient lesions will be performed to investigate signifying aberrant oncogene pathway(s) and their potential relationship to the study drug. For more information on the management of SCC, actinic keratosis, and keratoacanthomas, considered to be AESIs, see Section 7.9.

6.11.7. Clinical Laboratory Tests

Blood and urine samples will be collected according to Table 1 (schedule of assessments) 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 from the central laboratory 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 5.0.

Available local laboratory test results will be used for treatment management decisions (dose interruptions or dose modifications [Section 5.4.2]) and initial assignment of CTCAE grading. 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 Investigator should determine which laboratory values will be used for documenting grading of AEs. The local versus central laboratory result with the highest grade should be considered to document grading of AEs.

The safety laboratory tests are provided in Table 11.

Table 11: 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	
Thyroid Testing		
Thyroid stimulating hormone (TSH)		
Total triiodothyronine (T3)		
Total thyroxine (T4)		

1. For patients taking anticoagulants, testing will be performed according to Table 1 (schedule of assessments). 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.

6.11.8. Pregnancy Test

A serum β-hCG test to rule out pregnancy in women of childbearing potential will be obtained at screening and analyzed at the central laboratory. A urine pregnancy test will be completed at all other visits as outlined in Table 1 (schedule of assessments). A local serum pregnancy test may be performed instead of urine if it is the standard practice for the site 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 (amenorrhoeic for ≥ 12 months with a follicle stimulating hormone (FSH) ≥ 40 mIU/mL) or has documented complete oophorectomy or hysterectomy.

6.11.9. Contraception and Pregnancy Avoidance Measures

6.11.9.1. Contraception

The effects of DCC-2618 on sperm, conception, pregnancy, and lactation are not known. Participation in this study requires patients receiving DCC-2618 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 DCC-2618 and until 104 days following the last dose of DCC-2618.

Participation in this study requires patients receiving sunitinib to agree to use effective methods of contraception as per the approved package insert or institutional guidelines.

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 (e.g. 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 for at least 90 days previously
- Combined (estrogen and progestin containing) or progestin-only hormonal contraception associated with inhibition of ovulation:
    - oral
    - intravaginal
    - transdermal
    - injectable
    - implantable

NOTE: Hormonal contraceptives can be used as highly effective method of contraception unless they are one of the prohibited medications as described in Section 5.12.3.2 as the efficacy of the hormonal contraceptives may be affected due to potential drug-drug interactions with the study drug.

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 who are receiving DCC-2618 must not donate sperm after the first dose of study drug, throughout the study, and for 104 days following the last dose of DCC-2618. They should seek advice on conservation of sperm prior to the first dose of DCC-2618.
- Female patients and female partners of male patients who are receiving DCC-2618 must not plan to become pregnant during the study through 104 days following the last dose of DCC-2618.
- Female patients who are receiving sunitinib must not plan to become pregnant during the study through the last dose of sunitinib. Female partners of male patients receiving sunitinib must not plan to become pregnant during the study through the last dose of sunitinib.
- 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) for the duration of the study and until 104 days after the last dose of DCC-2618 or until the last dose of sunitinib.

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.

6.11.9.2. Pregnancy

Patients receiving DCC- 2618 must be counseled to inform the Investigator of any pregnancy that occurs during study treatment and for 104 days after the last dose of DCC-2618. Patients receiving sunitinib must be counseled to inform the Investigator of any pregnancy that occurs during study treatment. An exception is made for pregnancies that occur 104 days after the last dose of DCC-2618 or after the last dose of sunitinib 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 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 DCC-2618 or after the last dose of sunitinib. The Investigator must notify the Sponsor or designee within 1 business day of the site's knowledge of the patient's (or partner's) pregnancy. Instructions will be provided in the Study Reference Manual.

If the patient was receiving DCC-2618, the patient or female partner of the male patient 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.

6.11.10. 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.

6.11.11. 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), blood samples will be collected from patients receiving DCC-2618 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 5.3. 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 PK data from this study will be analyzed by population PK methods to generate PK parameters, which may be pooled with PK data from other DCC-2618 studies and may be reported separately from the primary results of this study. The population PK model will assess the effect of various covariates (e.g., age, sex, race, body weight, renal and hepatic function) on

the PK of both DCC-2618 and DP-5439 and generate exposures for exploration of exposure-response relationships for efficacy and safety.

[redacted]

6.14. Pharmacogenomic Measurements

6.14.1. Sample Collection

A pharmacogenomic sample will be collected at Cycle 1 Day 1 according to Table 1 (schedule of assessments). **South Korea Only:** Pharmacogenomic Samples will not be collected. 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 after the end of the study.

6.15. Healthcare Utilization

6.15.1. Healthcare Utilization Questionnaire (HCUQ)

The Healthcare Utilization Questionnaire (HCUQ) [See Appendix 17.2] was designed specifically 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). The required time for completion is approximately 3-5 minutes.

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 (e.g. 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 (e.g. 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 an 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 5.0, must be used for grading the severity of AEs (Cancer Therapy Evaluation Program website; available at: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0/.

The severity of an AE that does not appear in the CTCAE scale must be determined according to Table 12.

Table 12: Severity Grading Scale

Grade 1 (Mild)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 (Moderate)	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living.
Grade 3 (Severe)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care Activities of Daily Living.
Grade 4 (Life-threatening)	Life-threatening consequences; urgent intervention indicated.
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 13.

Table 13: 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 14.

Table 14: 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 15.

Table 15: 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 (e.g. urinary tract infection, anemia). In the absence of a diagnosis, the abnormal study assessment itself may be listed as the AE (e.g. 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 (i.e. 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 dose of study drug. 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 for Study Drug

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. AESIs 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 dose 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 (e.g. "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 (e.g. 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 Sponsor or designee **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 agencies 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 committees. 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. End of Treatment

A patient is free to withdraw from the study drug treatment 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 study drug treatment at any time if the patient's clinical condition warrants it. The primary reason for discontinuation or withdrawal of a patient from the study drug must be determined using the following categories:

- Clinical progression
- Progressive Disease by Independent Radiologic Review
- Progressive Disease by Investigator Assessment
- AE
- Withdrawal by patient from treatment
- Death
- Lost to Follow Up
- Non-compliance with study drug
- Physician decision
- Pregnancy
- Termination of Study by Sponsor
- Any other reason that in the opinion of the Investigator, would justify removing the patient from the study drug, based on the best interest of the patient

8.2. End of Study

The primary reason for discontinuation or withdrawal of a patient from the study must be determined using the following categories:

- Death
- Lost to Follow Up
- Termination of Study by Sponsor
- Withdrawal by patient from Study
- 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 OS and PFS2. Patients must return all used, partially used, and unused study drug bottles.

8.3. 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 426 patients (n=213 DCC-2618, n=213 sunitinib) was based on considerations for powering of the primary endpoint, secondary endpoints, detection of rare safety events and overall exposure to DCC-2618. Patients will be randomized in a 1:1 ratio of DCC-2618 versus sunitinib.

Under the assumptions that mPFS is 9 months for DCC-2618 and 6 months for sunitinib, the HR is about 0.667 for All Patients (AP) PFS (sunitinib vs DCC-2618). A total of 262 events will be required to achieve a statistical power of 90% to test the hypothesis of no difference between DCC-2618 and sunitinib in AP. Accrual of 426 patients (213 in DCC-2618 and 213 in sunitinib) within 21 months is expected to have 262 PFS events occurred after additional 8 months of follow up. This has accounted for 20% of dropout rate (discontinuation without progressive disease per IRR or death).

It is further assumed that the mPFS is 9 months for patients with a KIT Exon 11 primary mutation (Ex11) in DCC-2618 and 5 months for KIT Ex11in sunitinib, the HR is 0.556 for the KIT Exon11 PFS. It is planned to perform the final analysis on both KIT Ex11 and AP populations at the same time. The final analysis is planned to occur when at least 151 PFS events in KIT Ex11 population and approximately 262 PFS events in AP population have occurred. The 151 PFS events in KIT Ex11 population have at least 95% power to test the hypothesis of no difference between DCC-2618 and sunitinib in KIT Ex11 population.

9.2. Analysis Endpoints

9.2.1. Primary Endpoint

The primary and secondary efficacy endpoints will be analyzed for both the Ex11 ITT and AP ITT populations (see Section 9.3).

9.2.1.1. Efficacy

PFS based on independent radiologic review using modified RECIST (mRECIST) (Appendix 17.1). mRECIST 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 (e.g. 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. Key Secondary Endpoints

9.2.2.1. Efficacy

- ORR (confirmed CR + confirmed PR) based on independent radiologic review using mRECIST criteria
- OS

9.2.2.2. Other Secondary Endpoints

- QOL as measured by using EORTC QLQ-C30, DLQI, and the GP5 question from FACT-G
- TTP
- Disease control rate (DCR; CR + PR + SD) at 6, 9 and 12 months, based on independent radiologic review
- PFS based on investigator assessment
- Efficacy using Choi criteria based on independent radiologic review

9.2.2.2.1. Safety

Safety endpoints that will be evaluated include treatment-emergent adverse events (TEAEs), AESIs, SAEs, 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.

9.2.2.2.2. Pharmacokinetics

- Correlation of PK exposure with efficacy/safety
- Population-based PK parameters

9.2.3. Exploratory Endpoints

9.2.3.1. Efficacy

- QOL as measured by EQ-5D-5L, and the memory and concentration items from the PRO-CTCAE library
- PFS2: PFS on next line therapy based on local assessments
- Subgroup analysis for efficacy and other endpoints may be explored as data becomes available

9.2.3.2. Biomarkers and Pharmacodynamics

- Determine the potential innate and acquired resistance mechanisms to DCC-2618 in GIST.
- Assess KIT/PDGFRA mutations and mutant allele frequency at baseline and the treatment effect of DCC-2618 on KIT/PDGFRA mutant allele frequency
- Evaluate the association of anti-tumor activity/safety of DCC-2618 with the following:
    - baseline KIT/PDFGRA mutation status

- expression of KIT protein in tumor
- expression or polymorphic variation in drug metabolic and/or drug transporter genes

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:

- All Enrolled
- KIT Exon 11 Intent to Treat (Ex11 ITT)
- All Patients Intent to Treat (AP ITT)
- Safety
- PK
- KIT Exon 11 Per Protocol (Ex11 PP)
- All Patients Per Protocol (AP PP)

The all Enrolled Population is defined as all patients who signed the informed consent and met inclusion/exclusion criteria.

The KIT Exon 11 ITT (Ex11 ITT) Population is defined as all patients who are designated as having a mutation in KIT Exon 11 at the time of randomization. Patients in this population will be analyzed according to the treatment they were scheduled to receive.

The AP ITT Population is defined as all patients who are randomized. Patients in this population will be analyzed according to the treatment they were scheduled to receive.

The Safety Population is defined as all patients who are randomized and receive at least one dose of study drug. Safety population will be used for all safety analysis and treatment assignment will be based on the actual initial study treatment 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.

The KIT Exon 11 Per Protocol (Ex11 PP) Population is defined as the patients in the Ex11 ITT population with at least one post baseline tumor assessment who met all inclusion criteria, did not violate any exclusion criteria, and did not have any significant protocol violations/deviations considered to impact study integrity. The efficacy analysis on the Ex11 PP population is supportive and treatment group will be based on actual treatment received. Protocol violators resulting in exclusion from the PP population will be identified and documented prior to database lock.

Note: if a patient has a KIT exon 11 mutation, along with mutation(s) 1) in KIT exon 9 and/or PDGFRA, the patient will be randomized as having a KIT exon 11 mutation, unless the mutation allele frequency (MAF) data is available then the mutation with the higher MAF will be used to categorize the patient for the purposes of randomization; 2) in KIT other exon, the patient will be randomized as having a KIT exon 11 mutation.

The All Patients Per Protocol (AP PP) population is defined as all patients in AP ITT population with at least one post baseline tumor assessment who met all inclusion criteria, did not violate any exclusion criteria, and did not have any significant protocol violations/deviations considered to impact study integrity. The efficacy analysis on the AP PP population is supportive and treatment group will be based on actual treatment received. 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

Algorithms for imputing partial or missing dates are shown in Table 16. AE end dates are imputed to facilitate calculation of AE duration.

Table 16: 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 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.

9.5. Interim Analyses

No interim analyses are planned for the study.

9.6. Adjustment for Multiple Comparisons

To control familywise type-I error at 0.05 level, the hypothesis tests for treatment difference will be performed according to the hierarchical testing sequence below:

1. PFS in Ex11 ITT (two-sided 0.05 level)
2. PFS in AP ITT (two-sided 0.05 level)
3. ORR in Ex 11 ITT (two-sided 0.05 level)
4. ORR in AP ITT (two-sided 0.05 level)
5. OS in Ex11 ITT (two-sided 0.05 level)
6. OS in AP ITT (two-sided 0.05 level)

The testing starts from PFS in Ex11 ITT and each subsequent endpoint will only be tested if all the testing preceding to it have been statistically significant. If the testing for any endpoint fails to meet statistical significance, the testing and p-value for all the subsequent endpoints will be nominal and statistical significance won't be claimed for all the subsequent endpoints.

9.7. Blinding

This is an open-label study.

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, AEs, 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.

Unless specified, the ITT population is used for efficacy analysis and the safety population is used for the safety analysis. The primary and secondary efficacy endpoints will be analyzed for both the Ex11 ITT and the AP ITT populations.

9.8.2. Disposition of Patients

Patient disposition will be summarized overall for all patients who entered the study (i.e. signed the informed consent for the study and met inclusion/exclusion criteria). The number of patients in each population (enrolled, safety, PK, ITT, PP if applicable) and patients were removed from a population will be displayed. 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 (including risk assessment for recurrence at study entry) will be summarized by for the Safety, ITT, and PP populations (35).

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 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 for GIST, 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 in AP ITT will be stratified by the randomization stratification factors (mutation status [KIT exon 9 vs. KIT exon 11 vs. KIT/PDGFRA WT vs. other KIT {absence of exon 9 or 11}/PDGFRA] and intolerance to imatinib [yes vs. no]). Analysis for PFS in Ex11 ITT will be stratified by intolerance to imatinib [yes vs. no]. The p-value will be from a 2-sided stratified Log-rank test at 0.05 significance level for evaluation of treatment difference. Point estimate of hazard ratio will be obtained from a Cox regression model with treatment and the randomization stratification factors as fixed factors and the associated 95% CI will be obtained using the Wald method. Median progression free survival time (mPFS) with 95% confidence interval will also be presented by treatment using KM methodology.

NOTE:

Rules of defining PFS events and censoring PFS will be elaborated in the statistical analysis plan (SAP). Sensitivity analysis for PFS will be specified in the SAP.

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. Secondary Efficacy Endpoints

9.8.5.2.1. Objective Response Rate Analysis

ORR 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.

Analysis for ORR in AP ITT population will be stratified by the randomization stratification factors (mutation status [KIT exon 9 vs. KIT exon 11 vs. KIT/PDGFRA WT vs. other KIT {absence of exon 9 or 11}/PDGFRA] and intolerance to imatinib [yes vs. no]). Analysis for ORR in Ex11 ITT population will be stratified by intolerance to imatinib [yes vs. no]. For each population, the p-value will be based on a Cochran Mantel-Haenszel chi-square test for the association between treatment and ORR at 0.05 significance level; stratified Newcombe 95% confidence limits will be calculated for the difference in ORR between the treatment arms.

9.8.5.2.2. Overall Survival

OS 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. OS will be analyzed using similar model as PFS and will be analyzed based on both Ex11 ITT and AP ITT separately.

9.8.5.2.3. EORTC QLQ-C30

The EORTC QLQ C30 will be summarized by scales per the manual and treatments compared by role and physical function for both Ex11 ITT and AP ITT separately.

9.8.5.2.4. DLQI

The total score for the DLQI will be calculated by summing the score of each question for both Ex11 ITT and AP ITT separately, per the scoring manual (see http://sites.cardiff.ac.uk/dermatology/quality-of-life/dermatology-quality-of-life-index-dlqi/dlqi-instructions-for-use-and-scoring/). Higher scores are associated with a lower the quality of life. The total score will be summarized using descriptive statistics, including proportions who are moderately impacted (a total score of six to ten points) and severely impacted (a score of eleven or more). In addition to the total score, continuous descriptive statistics will also be displayed by section as follows:

Section	**Questions Included**
Symptoms and Feelings	1,2
Daily Activities	3,4
Leisure	5,6
Work and School	7
Personal Relationships	8,9
Treatment	10

9.8.5.2.5. GP5 Question from FACT-G

FACT-G: Functional Assessment of Cancer Therapy - General - is a validated and widely used questionnaire that can be used with cancer patients of any tumor type. It includes a question referred to as GP5 which asks, "I am bothered by side effects of treatment". The answer is provided by the patient who selects one of the following five choices: Not at all, A little bit, Some-what, Quite a bit, or Very much.

Effect sizes for the difference in mean GP5 scores between groups can be estimated as the mean difference divided by the pooled standard deviation. FACT-G will be summarized for both Ex 11 ITT and AP ITT separately.

9.8.5.2.6. Time to Tumor Progression

The secondary endpoint of TTP 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 for GIST, 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. TTP will be analyzed using similar model as PFS for both Ex 11 ITT and AP ITT separately.

9.8.5.2.7. Disease Control Rate Analysis

DCR will be calculated and summarized with n and percentage at 6, 9, and 12 months. Disease control will be defined as having a response (complete or partial) or SD. Fisher's Exact test will be used to investigate statistical differences between treatment groups for both Ex 11 ITT and AP ITT separately.

9.8.5.2.8. Progression-free Survival based on Investigator Assessment

PFS 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. Differences between treatment groups will be evaluated using the same methodology as for the primary endpoint for both Ex11 ITT and AP ITT separately.

9.8.5.2.9. Efficacy Based on Choi Criteria Based on Independent Radiologic Review

The primary PFS, ORR, TTP, and DCR analyses will be repeated using the Choi criteria in place of mRECIST for both Ex11 ITT and AP ITT separately.

9.8.5.3. Exploratory Endpoints

9.8.5.3.1. Memory and Concentration Items from PRO-CTCAE Library

The Memory and Concentration Items from the PRO-CTCAE Library will be summarized with n and percentage for each question.

9.8.5.3.2. 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 sunitinib. The EQ-VAS will be summarized using continuous descriptive statistics.

9.8.5.3.3. Efficacy

- Progression free survival on the next line of therapy (PFS2) will analyze time from the start of next therapy
- to the progression or death on the next line of therapy using the same methods used for the primary analysis of PFS.
- Subgroup analysis may be done as data becomes available.

9.8.5.3.4. Biomarkers and Pharmacodynamics

- Determine the potential innate and acquired resistance mechanisms to DCC-2618 in GIST.
- Assess KIT/PDFGRA mutations and mutant allele frequency at baseline and the treatment effect of DCC-2618 on KIT/PDGFRA mutant allele frequency.
- Evaluate the association of anti-tumor activity/safety of DCC-2618 with the following:
    - baseline KIT/PDFGRA mutation status
    - expression of KIT protein in tumor

- expression or polymorphic variation in drug metabolic and/or drug transporter genes

9.8.6. Safety Analysis

9.8.6.1. Adverse Events

AEs will be summarized utilizing the number of events and proportion of patients overall, by system organ class (SOC) 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 data listings will include all collected AEs.

AE toxicity grade will be classified using NCI-CTCAE Version 5.0 criteria (See Table 12). If a patient has multiple occurrences of the same SOC or preferred term, then only the most severe event will be summarized in the tables for that SOC and preferred term. AEs 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

Baseline, post baseline, and change at post baseline from baseline values will be summarized by time point utilizing descriptive statistics. 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 descriptive statistics. 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

Plasma concentrations of DCC-2618 and metabolite DP-5439 will be summarized utilizing continuous descriptive statistics, according to study visit and scheduled sampling time. In the event of dose modifications, plasma concentrations may also be summarized by dose level.

[redacted]

9.8.9. Pharmacogenomic Analysis

Pharmacogenomic analysis may be performed 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 (See Appendix 17.2) will be summarized using 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 independent data monitoring committee (IDMC) will monitor the safety and efficacy 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 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 ICH 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 authorities. 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, e.g. eCRFs and hospital records), all original signed ICFs, eCRFs, SAE forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g. 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 (e.g. 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 (28).

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 ICF must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The ICF 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 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, ICF, and other relevant documents, (e.g. 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 (e.g. FDA), the Sponsor's designated auditors, and the appropriate IRBs/IECs/REBs 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 (i.e. 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 (i.e. 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 (mRECIST)

mRECIST 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 (e.g. 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, Reichardt P, Kang YK, Blay JY, Rutkowski P,Gelderblom H, Hohenberger P, Leahy M, von Mehren M, Joensuu H, BadalamentiG, Blackstein M, Le Cesne A, Schöffski P, Maki RG, Bauer S, Nguyen BB, Xu J, Nishida T, Chung J, Kappeler C, Kuss I, Laurent D, Casali PG; GRID study investigators. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013 Jan26;381(9863):295-302.

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	□ □		