Clinical Study Protocol

Study Title:	A Multicenter Phase 2, Single-Arm Open-Label Study of DCC-2618 to Assess Efficacy, Safety, and Pharmacokinetics in Patients With Advanced Gastrointestinal Stromal Tumors Who Have Progressed On Prior Anticancer Therapies
Project No.:	ZL-2307-002
Version No. and Version Date:	30 October 2019/Version 1.0 (First Version) 14 September 2020/Version 2.0 (Revised according to the opinions on the investigator meeting)
Investigational Drug:	DCC-2618(ZL-2307)
Study phase:	Phase II Study
Sponsor:	Zai Lab (Shanghai) Co., Ltd.
Principal Investigator:	[redacted]

Signature page (Sponsor)

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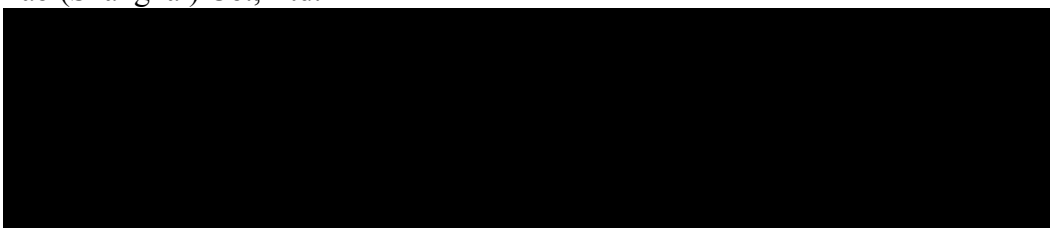


Protocol Synopsis

Sponsor/company name	Zai Lab (Shanghai) Co., Ltd.
Study Title	A Multicenter Phase 2, Single-Arm Open-Label Study of DCC-2618 to Assess Efficacy, Safety, and Pharmacokinetics in Patients With Advanced Gastrointestinal Stromal Tumors Who Have Progressed On Prior Anticancer Therapies
Protocol No.	ZL-2307-002
Study phase	Phase 2
Study site	Beijing Cancer Hospital, etc.
Principal Investigator	[redacted]
Planned number of subjects:	About 35
Study objectives	**Primary objectives:** To evaluate the progress free survival (PFS) of DCC-2618 in patients with advanced gastrointestinal stromal tumors who have progressed with prior anticancer therapies based on independent radiologic review. **Key secondary objectives:** To evaluate the objective response rate (ORR) of DCC-2618 in patients with advanced gastrointestinal stromal tumors who have progressed on prior anticancer therapies based on independent radiologic review. **Secondary objective:** To evaluate overall survival (OS) in DCC-2618-treated patients with advanced gastrointestinal stromal tumors who have progressed on prior anticancer therapies. To evaluate the pharmacokinetic (PK) profile of DCC-2618 in patients with advanced gastrointestinal stromal tumors who have progressed on prior anticancer therapies. To evaluate the safety of DCC-2618 in patients with advanced gastrointestinal stromal tumors who have progressed on prior anticancer therapies. **Exploratory objective:** To evaluate the efficacy of DCC-2618 in the patients when the dosage is increased to 150 mg BID.
Study design	This study is a multicenter phase 2, single-arm open-label study of DCC-2618 to assess efficacy, safety, and pharmacokinetics (PK) in patients with advanced gastrointestinal stromal tumors who have progressed on prior anticancer therapies. This study targets at the patients with advanced gastrointestinal stromal tumors who have progressed on prior anticancer therapies. It is planned to enroll about 35 subjects in total. Prior anticancer therapies must include imatinib, sunitinib, and one or two other drugs, and the number of patients who have previously received treatment with ≥ fourth-line drugs should be 40% or less.

	In this study, progression free survival (PFS) based on independent radiologic review is the primary efficacy indicator and RECIST v1.1-GIST Specific Standard is used for tumor efficacy assessment. After being fully informed, signing the informed consent forms and passing the screening, the subjects will receive DCC-2618 (150 mg, QD) continuously until the occurrence of an event for treatment termination as specified in the protocol, 28 days as a treatment cycle, followed by a safety follow-up period until 30 days after the termination of study treatment. During the study period, the subjects will be subject to visits as scheduled in the protocol. On the day of the scheduled visit as per the protocol, the subjects should bring the drug to the study site, where they will complete all the pre-dose examinations, and take the drug of the day after being suitable to continue the administration, in the discretion of the investigator. In the first four cycles (inclusive), an radiographic examination will be performed within ±7 days of each cycle and tumor efficacy will be assessed according to RECIST v1.1-GIST Specific Standard. After that, it should be performed within ±7 days every two cycles. If the subject discontinues treatment for reasons other than progressive disease, death, withdrawal of informed consent and lost to follow-up, the subject should receive radiographic examination for tumor assessment by independent radiologic review (IRR) after treatment withdrawal according to the frequency consistent with that during the study until presence of disease progression meeting "RECIST v1.1-GIST Specific Standard" or until starting of new anti-tumor therapy, whichever is the first. Based on independent radiologic review, if a subject has a radiologically confirmed progression disease (PD), the subject can choose: ○ To continue DCC-2618, at an increased dose of 150 mg BID, until the occurrence of an event for treatment termination as specified in the protocol; in the case of the efficacy evaluation for such patient, the lesion diameter before the increase of dosage (but not screening period) should be taken as the baseline value. ○ To continue DCC-2618 at a dose of 150 mg QD, until the occurrence of an event for treatment termination as specified in the protocol, if the subject can benefit from the treatment with DCC-2618, but cannot tolerate the increase of dosage, after being fully assessed by the investigator; ○ To terminate the treatment with DCC-2618. In the study, intensive blood collection is only necessary for the first 10-15 enrolled subjects, and for the rest, they will receive sparse blood collection. After PK sampling, the subjects can continue the treatment with DCC-2618, safety visits and efficacy evaluation, until the occurrence of an event for treatment termination as specified in the protocol. Treatment suspension or dosage reduction or treatment withdrawal is allowed at any time during the study for subjects with an intolerant toxicity reaction.
Inclusion Criteria:	The eligible subjects for this study must meet all of the following inclusion criteria:

	1. Male or female patients ≥18 years of age. 2. Patients with histopathologically-confirmed advanced gastrointestinal stromal tumors. 3. Subjects who have progressed on previous treatments with imatinib, sunitinib and one or two other drugs or have documented intolerance to any of these treatments. Note: A documented intolerance must be after the dosage adjustment (including suspension and reduction). 4. ECOG PS of 0-2. 5. 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 investigational drug. 6. Patients of reproductive potential must agree to follow the contraception requirements. 7. Patient is capable of understanding and complying with the protocol. Signed written informed consent before any study-related procedures were performed. 8. Subject must have at least 1 measurable lesion (non-nodal lesions must be ≥ 1.0 cm in the long axis or ≥ 2 times the slice thickness) according to the RECIST v1.1-GIST Specific Standard. A lesion with definite progression after local treatment can also be considered to be measurable. Radiographic examination results must be available within 21 days prior to the first dose of the investigational drug. 9. Good organ function and bone marrow reserve function, including: ● Neutrophil count ≥ 1,000/μL ● Hemoglobin ≥ 8 g/dL ● Platelet count ≥75,000/μL ● Total bilirubin ≤1.5*the upper limit of normal (ULN) ● AST and ALT ≤3*ULN, and AST and ALT≤5*ULN in the presence of hepatic metastases ● Serum creatinine ≤1.5*ULN or creatinine clearance ≥50 mL/min (based on Cockcroft-Gault estimation) Formulas for calculation: Note: within 2 weeks prior to the above laboratory assessments, patients should not receive granulocyte colony-stimulating factor, interleukin-11 or infusion of red blood cells or platelets or other blood products. ● Prothrombin time (PT) or international normalized ratio (INR) or partial thromboplastin time ≤1.5 × ULN. Patients on a stable, maintenance regimen of anticoagulant therapy for at least 30 days prior to investigational drug administration may have PT/INR measurements >1.5 ×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 baseline) within

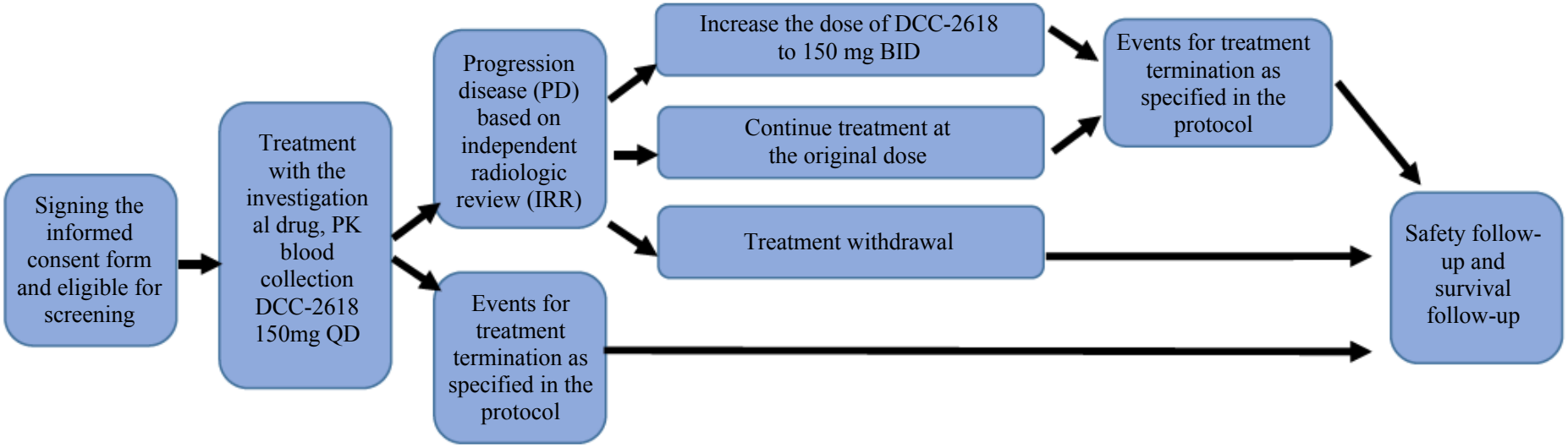
	1 week prior to the first dose of investigational drug (excluding alopecia and ≤ Grade 3 clinically asymptomatic lipase, amylase, and creatine phosphokinase laboratory abnormalities).
Exclusion Criteria:	Subject meeting any of the following criteria should not be enrolled in this study: 1. Treatment with anticancer therapy, including investigational therapy, or investigational procedures within 14 days or 5 x the half-life (whichever is longer) prior to the first dose of investigational drug. For prior biological therapies, eg, monoclonal antibodies with a half-life longer than 3 days, the interval must be at least 28 days prior to the first dose of investigational drug. 2. Prior treatment with DCC-2618. 3. Previously or currently has an additional malignancy that is progressing or required active treatment, which may interfere with the safety or efficacy evaluation of DCC-2618. If the patient is receiving the adjuvant therapy that is likely to be effective for GIST or should be excluded based on the protocol (see Section 5.9.3), the patient should not be included in this study. 4. Patient has known active central nervous system metastases. 5. New York Heart Association class II - IV heart disease, active ischemia or any other uncontrolled cardiac condition such as angina pectoris, clinically significant cardiac arrhythmia requiring therapy, uncontrolled hypertension or congestive heart failure. 6. Arterial thrombotic or embolic events such as cerebrovascular accident (including ischemic attacks) or hemoptysis within 6 months before the first dose of investigational drug. 7. Venous thrombotic events (eg, deep vein thrombosis) or pulmonary arterial events (eg, pulmonary embolism) within 3 months before the first dose of investigational drug. Patients with venous thrombotic events ≥3 months before the first dose of investigational drug on conventional anticoagulation therapy are eligible. 8. 12-lead electrocardiogram (ECG) demonstrating QT interval corrected by Fridericia's formula >450 ms in males or >470 ms in females at screening or history of long QT interval syndrome. 9. Left ventricular ejection fraction (LVEF) <50% at screening. 10. Use of strong or moderate inhibitors and/or inducers of cytochrome P450 (CYP) 3A4, including certain herbal medications (eg, St. John's Wort) and consumption of grapefruit or grapefruit juice within 14 days or 5 x the half-life (whichever is longer) prior to the first dose of investigational drug. 11. Use of known substrates or inhibitors of breast cancer resistance protein (BCRP) transporters within 14 days or 5 x the half-life (whichever is longer) prior to the first dose of investigational drug. 12. Major surgeries (eg, abdominal laparotomy) within 4 weeks of the first dose of investigational drug; Following major surgeries, >4 weeks prior to the first dose of investigational drug, all surgical wounds must be healed and free of infection or dehiscence. 13. 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. 14. Active viral infections such as human immunodeficiency virus, hepatitis B, hepatitis C infection, etc. 15. Female patients who are pregnant or lactating or who are expected to become pregnant during the study treatment period 16. Known hypersensitivity to any component of the investigational drug. Patients with Stevenson Johnson syndrome in previous TKI treatment need to be excluded. 17. Gastrointestinal abnormalities including but not limited to: ● inability to take oral medication ● malabsorption syndrome ● Requiring intravenous nutrition 18. Any active hemorrhages, excluding hemorrhoids or gum bleeding.
Investigational Drug	Drug: DCC-2618 Dosage form: Tablet Dosage: 150 mg QD Administration route: oral
Study endpoints	**Primary endpoints:** Progression-free survival (PFS): based on independent radiology review using "RECIST v1.1-GIST Specific Standard" which includes: ● Lymph nodes cannot be taken as target lesions; enlarged lymph nodes will be followed as non-target lesions. ● Bone lesions cannot be taken as target lesions; ● Positron emission tomography (PET) cannot be used in efficacy assessment; ● According to "RECIST v1.1-GIST Specific Standard", new tumor nodules within the pre-existing tumor lesion that are gradually growing must meet the following criteria before being determined as definite progression: (a) The lesion diameter should be at least 2 cm and confirmed as active GIST lesion (for example, using contrast or other criteria for enhanced scanning to rule out the possibility of false appearance); Or (b) At least 2 consecutive radiographic examinations indicative of enlarged lesion. **Key secondary efficacy indicator:** Objective response rate (ORR) as determined by confirmed CR + confirmed PR by independent radiologic review **Secondary efficacy indicator** ● Overall survival (OS)

	● Time to best response (TBR) based on independent radiologic review ● PFS based on investigator's assessment ● Disease control rate (DCR, CR+PR+SD) on Week 12 based on independent radiologic review **Safety:** ● Incidence and severity of treatment emergent adverse event (TEAE), adverse event of special interest (AESI) and serious adverse event (SAE) during the study (including intensive blood collection); severity will be assessed based on NCI-CTCAE V4.03. ● Incidence of adverse events resulting in dose reduction, suspension and termination of the investigational drug; ● Changes from baseline in ECOG score, vital signs, ECG, left ventricular ejection fraction, dermatological examination and laboratory parameters. **Pharmacokinetic profile:** ● The PK parameters will be calculated according to the plasma concentration of DCC-2618 and the metabolite DP-5439, including but not limited to C_{max}, T_{max}, AUC and $T_{½}$, etc. **Exploratory indicator:** PFS2 based on investigator's assessment: the duration from the date of the first dose of the investigational drug (150 mg, BID) after the dose is increased to 150 mg to the date of first recording tumour progression after increasing the dose or the date of death for any reasons, whichever occurs first.
Statistical Analysis	● Single-arm, open-label study: ● Primary efficacy indicator is the PFS based on independent radiologic review: ● Calculation of sample size: This phase 2 bridging study is to prove the efficacy of DCC-2618 in Chinese patients is consistent with or similar to that in global patients using the primary endpoint of progression-free survival (PFS) on the basis of independent radiologic review. Standard definition of bridging study success (consistent or similar): mPFS of ripretinib in Chinese patients will be statistically longer than 1 month, that is, the lower limit of bilateral 90% confidence interval of the observed mPFS is longer than 1 month. Statistical hypothesis: H_0: mPFS is 1 month; H_a: mPFS is 2.5 months; bilateral significant level is 0.1; assumed enrollment duration is 6 months; follow-up duration is 2 months; drop-out rate is 15% under at least a 90% test power; approximately 35 subjects should be enrolled to satisfy test purposes. All statistical analysis will be programed and calculated using SAS9.2 software or higher. The results of this study mainly adopt statistical description method. The measurement data are expressed as the mean, standard difference, median, maximum and minimum; Enumeration data and ranked data are expressed as the frequency (constituent ratio), rate and confidence interval.

	During the study (including intensive blood collection period), the TEAEs and drug combination, clinical laboratory parameters, vital signs, ECG and UCG will be summarized according to the study visits and the analysis will present the observations from each visit in the trial and its changes from baseline. The PK parameters of DCC-2618 and its metabolite DP-5439 are calculated by WinNonlin 7.0 or higher with non-compartment model for patients after a single and multiple doses, and descriptive statistics are made for PK parameters obtained from the calculation.
Study duration	The study will be terminated when the last subject has been enrolled for 2 years or after the last visit of the last subject or on the sponsor's decision, whichever is the first. For patients still taking investigational drug after the clinical trial database has been closed, if the investigator thinks that they can get continuous clinical benefit and if the sponsor agrees, those patients may continue taking DCC-2618 until presence of disease progression, death, or intolerable toxicity, or their demand to discontinue treatment. Such patients will only be monitored for all serious adverse events until 30 days after the last dose of the investigational product or the initiation of new anti-tumor therapies (whichever is the first).
Schedule of visits and the content thereof	Please refer to Table 1

Figure 1 Study Diagram



Note: Based on IRR, continued treatment with an increase to 150 mg BID or with the original dosage should not be provided for a patient after the first PD, unless he or she is evaluated by the Investigator as able to tolerate. The diameter of the lesion before the increase of dosage (other than that during the Screening Period) should be used as baseline diameter when the effect on the patient after dose up-titration is evaluated.

Table 1: Schedule of Study Visits

Evaluation/procedure[1]	Screening period[2]	Single-dose PK blood sampling	C1	C1	After C2	Termination of study treatment	Follow-up period (30 days after the last dose)	OS follow-up[3]
Cycle/day	-28 ~ -8	-7 ~ -1	1 (baseline)	15 (±1 day)	1 (±3 day)	Within 7 days after the last dose	(±5 days)	Every month (±5 days)
Site visit	X	X	X	X	X	X		
Telephone follow-up							X	X
Informed consent	X							
Inclusion/exclusion criteria	X							
Demographics	X							
Past medical history and tumor history	X							
Previous medications/treatment operation[4]	X							
Serum/urine pregnancy test[5]	X		X		X	X		
Laboratory test								
Hematology	X		X	X	X	X		
Blood biochemistry	X		X	X	X	X		
Blood coagulation function[6]	X		X	X[6]	X	X		
Urine routine[7]	X				X[7]	X		
Thyroid function test			X					
Physical examination	X[8]	Perform examination according to clinical findings and/or subject's complaints						
ECOG score[9]	X		X	X	X	X		
Vital signs and body weight[10]	X		X	X	X	X		

Evaluation/procedure[1]	Screening period[2]	Single-dose PK blood sampling	C1	C1	After C2	Termination of study treatment	Follow-up period (30 days after the last dose)	OS follow-up[3]
Cycle/day	-28 ~ -8	-7 ~ -1	1 (baseline)	15 (±1 day)	1 (±3 day)	Within 7 days after the last dose	(±5 days)	Every month (±5 days)
Site visit	X	X	X	X	X	X		
Telephone follow-up							X	X
Height	X							
12-lead ECG [11]	X		X		X	X		
Echocardiography[12]	X				X[12]	X		
Dermatologic examination[13]	X				X[13]	X		
Ophthalmological examination[14]	X							
AE evaluations	From signing an ICF to the end of the safety follow-up							
Enquire about concomitant medications/treatment operation	From the first dose to the end of the safety follow-up							
DCC-2618 dosing[15]			X	X	X			
DCC-2618 dispensing and recovery			X		X	X		
PK sampling[16]		X	X	X	X			
Radiographic examination[17]	X				X			
Survival follow-up								X

1. All evaluations must be completed before administration unless specified otherwise. The Investigator may prescribe relevant additional examinations at any time as clinically indicated.
2. The Screening Period covers 21 days from Day -28 to Day -8. Radiographic examination must be performed within 21 days before the first dose of drug. Radiographic examination performed before signing an ICF can be used in the Screening Period as long as it is performed within 21 before the first dose and the examination method and result comply with the protocol.
3. Survival follow-up will be given to all subjects, until withdrawal of ICFs or lost to follow-up or death due to any cause. After the end of the safety follow-up,

survival follow-up visits will be made by phone on a monthly basis (±5 days).

4. The collection of previous medications starts 30 days before the signing of ICFs. The history of tumor treatment needs to be collected from the time when the tumor is first diagnosed.
5. Serum pregnancy test needs to be performed on women of childbearing age within 7 days before the first dose, which is to be followed by a urine pregnancy test on Day 1 of each cycle as well as at the end of the study treatment, for confirmation of a negative result.
6. For patients taking anticoagulants, coagulation tests will be performed according at C1D15 visit. During the study treatment, the blood coagulation function must be monitored according to appropriate clinical needs in case of any change in the dosage of anticoagulants.
7. Urinalysis will be performed during the Screening Period, on C2D1, C3D1, C4D1 as well as at the end of the study treatment.
8. A general physical examination is required during the Screening Period:
9. During the study treatment, ECOG score can be rated before or after administration.
10. Data on vital signs must be collected at least 5 minutes after the patient has a rest (in a sitting or supine position). Additionally, weight data must be collected at each visit.
11. 12-lead ECG must be performed at least 15 minutes after the patient has a rest (in a supine or semi-recumbent position).
12. Echocardiography only needs to be performed during the Screening Period, C3D1, once in every three cycles (Cycles 6, 9, 12, etc.) and at the end of the study treatment. Additional ones may be performed during the study treatment as clinically indicated. If the ECG is performed before signing an ICF, it can be used as one performed during the Screening Period provided that the examination is performed within 21 before the first dose and as per the protocol.
13. Dermatological examinations only need to be performed in the Screening Period, at C3D1, and then once every three cycles (Cycles 6, 9 and 12, etc.) and at the end of the study treatment. Additional ones may be performed as clinically indicated. The examinations must cover the whole skin. Special attentions should be paid to squamous cell carcinoma of skin, actinic keratosis and keratoacanthoma. If the dermatological examination is performed before signing an ICF, it can be used as one performed during the Screening Period provided that the examination is performed within 21 before the first dose and as per the protocol. Dermatological examinations may be performed within 7 days before the follow-up visit or after the administration on the date of the follow-up visit.
14. Ophthalmological examination can be performed during the Screening Period or as clinically indicated only. Ophthalmological examination may not be repeated during the Screening Period, provided that it has been performed within 28 days before signing an ICF on the patient who discontinued previous anti-tumor therapy, with the examination report available, and that the examination conforms to the requirement of the protocol.
15. Administration: For patients who take part in intensive blood collection, blood samples need to be collected on D-7 first, which is followed by administration of one dose of the drug, and then intensive blood sample collection without taking the investigational drug until D-1. Collect blood sample once first on C1D1, which is to be followed by continuous administration with investigational drug from C1D1. The investigational drug should be taken at the same time each day as far as possible during the study. On the visit date, subjects need to bring their medication to the study site and not to take the investigational drug until the pre-dose assessments are completed.
16. Refer to Section 6.12 of the text on Intensive and Sparse Blood Collection Time Points. Unscheduled blood collection may be requested by the Sponsor at the

time of certain AEs that are possibly related to treatment.

17. Radiographic examination during the Screening Period should cover the chest, the abdomen and the pelvis (within 21 days before the first dose). Only abdomen and pelvis are examined during the study; for patients with pulmonary metastases in the screening period or pulmonary metastases symptoms during the study at the investigator's discretion, chest examination should be performed during the study. It is performed once in each of the first four cycles (including Cycle 4), and then once in every two cycles (e.g., Cycles 6, 8 and 10). Initial evaluation of CR or PR should be conformed 4 weeks later at least. Enhanced scanning is required for the examination. MRI may be applied to subjects allergic to CT enhancer to examine the abdomen and the pelvis, with plain CT scanning for the chest. Ensure consistency in examination means during the study. No ultrasonic examination is allowed. If the subject discontinues treatment for reasons other than progressive disease, death, withdrawal of informed consent and lost to follow-up, the subject should receive radiographic examination for tumor assessment by IRR after treatment withdrawal according to the frequency consistent with that during the study until presence of disease progression meeting "RECIST v1.1-GIST Specific Standard" or until starting of new anti-tumor therapy, whichever is the first.

Table of Abbreviations and Definitions of Terms

Abbreviations	Chinese Terminology
AE	Adverse Event
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Neutrophil count
APTT	Activated partial thromboplastin time
ASM	Aggressive systemic mastocytosis
AST	Aspartate aminotransferase
ATC	Chemical drug classification system
AUC	Area under the concentration-time curve
β-hCG	Human Chorionic Gonadotropin
BCRP	Breast cancer resistance protein
BID	Twice daily
BP	BP
CI	Confidence interval
CL/F	Apparent plasma clearance
C_{max}	Maximum concentration
CPK	Creatine kinase
CR	Complete response
CSF1R	Macrophage colony stimulating factor receptor
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DCR	Disease control rate
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EOT	End of Study Treatment
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration

Abbreviations	**Chinese Terminology**
GCP	Good Clinical Practice
GGT	Glutamyl transpeptidase
GIST	Gastrointestinal stromal tumor
HDPE	High-density polyethylene
HIV	Human immunodeficiency virus
HR	Hazard ratio
ICF	Informed Consent Form
IEC	Independent Ethics Committee
ICH	International Conference on Harmonization
INR	International Normalized Ratio
IRB	Institutional Review Board
IRR	Independent Radiologic Review
IWRS	Interactive web response system
KIT	cKIT proto-oncogene
LVEF	Left ventricular ejection fraction
MCL	Hypertrophy cell leukemia
MedDRA	Medical Dictionary for Regulatory Activities
MDR	Multidrug resistance protein
MPN	Myeloproliferative neoplasm
MRI	Magnetic Resonance Imaging
NADPH	Nicotinamide adenine dinucleotide phosphate
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NOAEL	No observed adverse effect level
ORR	Objective response rate
OS	Overall survival
PD	Disease progression
PDGFRA	Platelet-derived growth factor receptor α
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
QD	Once daily

Abbreviations	**Chinese Terminology**
QTc	Corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase II Dose
SAE	Severe adverse events
SAP	Statistical Analysis Plan
SD	Stable disease
SM	Systemic mastocytosis
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Half-life
FT3	Tri-iodothyronine free
FT4	Free thyroxine
TEAE	Treatment-emergent adverse events
T_{max}	Time to maximum observed drug concentration
TSH	Thyrotropic hormone
ULN	Upper limit of normal
Vd/F	Apparent volume of distribution at the terminal phase
VEGFR2	Vascular endothelial growth factor 2

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1 INTRODUCTION AND RATIONALE

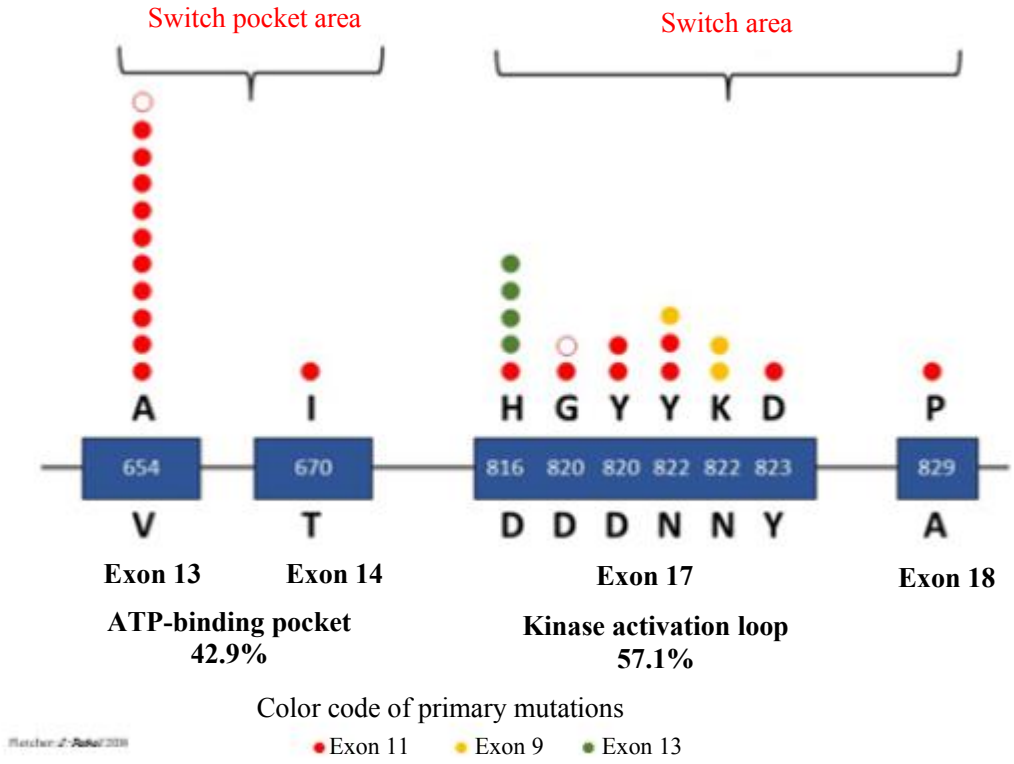
1.1 INTRODUCTION

Studies showed that mutations of proto-oncogene cKIT (KIT) and/or platelet-derived growth factor receptor α (PDGFRA) exist in various types of cancers, such as gastrointestinal stromal tumor (GIST), melanoma subtype, seminoma, and acute myeloid leukemia (AML), and myeloproliferative neoplasm (MPN) such as systemic mastocytosis (SM) including aggressive SM (ASM) and mast cell leukemia (MCL)[2, 3, 4, 5, 6]. Studies also revealed that GIST, melanoma, AML, glioma, and neuroendocrine tumor presented abnormal wild-type KIT and/or PDGFRA over-expression[7, 8, 9, 10].

GIST is induced by activated mutation in KIT (about 80%) or relevant PDGFRA (about 10%) receptor tyrosine kinase[1, 2, 3]. Generally, KIT exons 9 or 11 mutation was found in patients with GIST. Primary exon 11 mutation destroys autoinhibitory domains of kinase and primary exon 9 mutation increases receptor dimerization. Both mechanisms lead to ligand-independent receptor activation, making the growth and transformation of cells out of control. Multiple KIT target treatments have been approved for the treatment of GIST, but the efficacy is limited.

After receiving target therapy, secondary drug-resistant KIT mutations often occur in catalytic domains of kinase and these mutations usually map to interconversion and control mechanism of embedded conformations that regulate KIT activity. (Figure 2). Secondary KIT mutations usually occur in exons 13 and 14 (approaching adenosine triphosphatase [ATP]-binding pocket and in conformational switch control pocket), and destroy drug binding capacity in space or activate KIT conformation. These mutations can also occur in the activation loop (conformational control switch) encoded by exons 17 and 18[11, 12]. Activation loop mutation can transform kinase into activation conformation, making it difficult to bind to the approved therapeutic drugs[13]. Other diseases harboring primary KIT (or PDGFRA) activation loop mutations include SM, AML and PDGFRA-induced GIST[7, 14, 15].

Figure 2 Various secondary KIT mutations in cross-exon 13 - 18 in GIST patients (N = 27)



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.

At present, multiple target therapeutic drugs have been approved for the treatment of advanced GIST. The first-line therapeutic drug imatinib is the first FDA-approved KIT inhibitor and was approved in 2002 for the treatment of advanced GIST[16]. However, it is usually incurable, with a complete response (CR) rate of 5% and objective response rate (ORR) of 68%[17]. More than 80% GIST patients can benefit from imatinib monotherapy, but it is inevitably to have secondary drug resistance. More than half of the patients would experienced disease progression within 2 years[18]. Progression is likely to be related to secondary mutation in KIT kinase domains that result in imatinib resistance[12]. Although imatinib has a good efficacy in patients with KIT exon 11 mutation and an increased dose to 800 mg also presented certain efficacy in patients with KIT exon 9 mutation, but for other KIT exon mutations or PDGFRA mutations, the efficacy is either weak or none[18, 19].

Sunitinib was approved by FDA in 2006 for the treatment of advanced GIST patients who do not respond to or can't tolerate imatinib. Compared with imatinib, sunitinib shows a good efficacy in GIST patients with KIT exon 9 mutation and a weak efficacy in GIST patients with KIT exon 11 mutation[15, 18]. In addition, sunitinib presented anti-tumor activity to KIT exons 13 and 14, but only half of the patients benefited from it, with a median progression-free survival (mPFS) of 5.5 months[18]. Sunitinib was ineffective in patients with

KIT exons 17 and 18 mutations and PDGFRA exon 18 mutation.

Regorafenib was approved by FDA in 2013 for the third-line treatment of adult patients with unresectable and/or metastatic GIST after failure of imatinib and sunitinib and could significantly prolong patients' overall survival. Besides being effective in patients with KIT exon 11 mutation, regorafenib is the only approved drug targeting KIT exon 17 mutation and mPFS in patients with response was nearly 5 months. However, some patients were resistant to regorafenib due to secondary KIT mutations[12].

Complex heterogenicity of KIT mutations in individual patient is the major reason for drug resistance[12]. Therefore, a broad-spectrum kinase inhibitor that can inhibit multiple KIT mutations in individual patient has a very high treatment value in relapsed GIST patients. What's more, it is an important treatment objective to confirm whether DCC-2618 can delay the occurrence of KIT mutations leading to drug resistance.

At present, no broad-spectrum inhibitor has been approved for marketing against secondary KIT mutations leading to drug resistance. Therefore, it is urgent to develop a kinase inhibitor targeting multiple KIT and PDGFRA mutations.

At present, imatinib, sunitinib and regorafenib have been approved in China for the treatment of unresectable and/or metastatic GIST patients. The main data supporting the approval of regorafenib in China are from a global, international, multicenter, phase 3, randomized, controlled, double blind study where 199 patients were included, including 11 Chinese patients. Due to limited sample size, Chinese patients were not analyzed independently. Up to now, regorafenib has not been widely used as third line therapy in Chinese GIST patients. GIST patients are facing difficulties of out of medication after failure of imatinib and sunitinib. Patients have to enter the follow-up period for disease monitoring and passively wait for unavoidable disease recurrence. Therefore, it is still an urgent and important clinical project to research and develop new target drugs that target GIST drug resistance mechanism, prolong disease control, and delay recurrence and to excavate molecular markers of significance to prognosis prediction.

1.2 Intended Indication

DCC-2618 is a orally administered KIT/PDGFRA kinase inhibitor, developed by Deciphera, used to treat KIT/PDGFRA-driven GIST and other proto-oncogene tyrosine kinase-driven malignant tumors. DCC-2618 can not only inhibit KIT and PDGFRA but also inhibit macrophage colony stimulating factor receptor (CSF1R, also known as FMS), vascular endothelial growth factor receptor 2 (VEGFR2) and endothelial tyrosine kinase receptor TIE2. According to literatures, these substances seldom induce tumor progression, but are associated with tumor growth.

Gastrointestinal stromal tumor is a disease seriously threatening human health and is the most common mesenchymal cell tumor of the gastrointestinal tract[20], accounting for 1% - 3% of

malignant gastrointestinal tumors. The annual incidence in China is 4.3 - 22 out of 1,000,000 persons[21, 22]. There are about 3000 - 6000 new GIST cases every year in American adults[23, 24, 25]. GIST often occurs in population who are older than 50 years of age, mostly between 55 - 65, and there is no significant difference in incidence between males and females[26]. For local GIST, surgical resection is the basic treatment approach. For metastatic or unresectable GIST, radiotherapy and conventional chemotherapy are basically ineffective[20, 27]. About 50% GIST patients would have metastasis at the first diagnosis. Imatinib, sunitinib and regorafenib have opened a era of target therapy for GIST, but are difficult to realize complete response[20]. Similar to the target therapies for other tumors, most patients would experience drug resistance within months to years of treatment[23].

1.2.1 Non-clinical Summary

Refer to the Investigator's Brochure for detailed information on nonclinical studies.

1.2.1.1 Pharmacology

Recombinant kinase test and cell test were carried out with drug-resistant cell lines of GIST patients, cell lines of acute myeloid leukemia (AML) and mastocytosis or cell lines transfected with KIT or PDGFRA mutants, so as to conduct in vitro evaluation of DCC-2618. The above study revealed that DCC-2618 can comprehensively inhibit clinically significant KIT and PDGFRA mutations that can’t be treated with or don’t respond to the current therapies. Evaluation results of tumor cell lines provide guidance for further in vivo assessment of refractory/drug-resistant tumor xenograft models.

In vivo pharmacology of DCC-2618 was evaluated in several tumor models: efficacy was evaluated in human xenograft model in nude mice; PK/PD study was carried out in tumor-bearing mice to assess the necessary exposure of DCC-2618 for persistent inhibition of KIT mutations.

In vivo, DCC-2618 presented potent antitumor activity in GIST model carrying KIT mutation. Moreover, DCC-2618 can also effectively inhibit KIT phosphorylation in GIST model.

PK/PD study in human GIST xenograft model in mice indicated that after a single dose of 50 mg/kg, exposure of DCC-2618 was 2500 ng*hr/mL (including after active metabolite DP-5439, exposure was 5000 ng*hr/mL); inhibition rate against KIT was 69 - 88% within 8 hours after administration and about 40% 12 hours after administration. In GIST T1 model, after administration at 50 mg/kg twice daily (BID), combining exposure ($AUC_{0\text{-}24hr}$) of DCC-2618 and metabolite DP-5439 was 10,000 ng*hr/mL and tumor inhibition rate reached 90%. Exposure measured in the PK/PD study is used to guide the confirmation of toxic products that can reach several times the above exposure for persistent KIT inhibition.

Hepatocellular metabolite identification study indicated that the main metabolic pathway of DCC-2618 is active metabolite named DP-5439 formed by N-demethylation. In preclinical studies in animals, significant fraction of DP-5439 was detected in plasma of mice, rats and

dogs. Yield of the metabolite was highest in mice. PK parameters showed that in terms of $AUC_{0\text{-}24hr}$, DP-5439 exposure in mice was equivalent to DCC-2618 exposure. Total active drug exposure of ($AUC_{0\text{-}24hr}$) was calculated based on the combining exposure of DCC-2618 and metabolite DP-5439. After single-dose oral administration at 50 mg/kg, total active drug exposure of in mice was 5000 ng*hr/mL; after administration at 50 mg/kg twice daily (BID), combining exposure of DCC-2618 and metabolite DP-5439 ($AUC_{0\text{-}24hr}$) was 10,000 ng*hr/mL, which has reference value for non-clinical safety study and analysis. Metabolite DP-5439 was also detected in a phase 1 ascending dose study. At a clinically effective dose, exposure of metabolite was higher than DCC-2618 exposure.

Efficacy and tolerability observed in these model systems support the clinical development of DCC-2618.

1.2.1.1.1 Safety pharmacology

Binding of DCC-2618 to human ether-à-go-go related gene (hERG) potassium channel components can be ignored.

DCC-2618 at 15, 60 or 300 mg/kg was administered to rats and it did not have influence on any combination items of modified behavior Irwin test combination at all measuring time points. When the administration dose was 15 mg/kg, tidal volume of rats decreased by 10%; when the dose was 300 mg/kg, it decreased by 17%. Physiologically, the observed tidal volume was of no significance because these changes were temporary and not significant.

A 4-week multiple-dose toxicological study was carried out in dogs, and cardiovascular safety was assessed by measuring their electrocardiogram (ECG), blood pressure and troponin I levels. The study showed that the investigational drug did not have significant impact on blood pressure, heart rate, ECG intervals, and troponin I level. In an independent cardiovascular safety study, after investigators gave single dose of DCC-2618 to Beagle, diastolic blood pressure and mean arterial pressure of Beagle (2 - 6 hours after administration) increased, which was generally related to the expected time to maximum plasma concentration (T_{max}). At doses of 7, 20 and 75 mg/kg, the diastolic blood pressure was higher than that of the control group (higher by 12%, 12% and 17%, respectively), the mean arterial pressure was higher than that of the control group (higher by 12, 10 and 14 mmHg at most, respectively); there was no change in systolic blood pressure or arterial pressure.

In the later stage of the study, that is, 9 - 19 hours after administration, heart rate increase was observed, and QT interval and PR interval shortened (likely to be second to heart rate changes); there was no change in QTc interval. In the whole later stage, heart rate increased. At doses of 7, 20 and 75 mg/kg, the maximum difference occurred within 13 - 17 hours after administration; heart rate was higher by 45%, 70% and 129% than the control group in the same period, respectively. At present, mechanism of these changes is unknown; blood pressure and heart rate will be closely monitored in the clinical trial. Although attentions

should be paid to change degree of blood pressure and heart rate, this does not mean the investigational drug has severe toxicity.

1.2.1.2 Pharmacokinetics and absorption, distribution, metabolism and excretion

In vitro and in vivo studies were carried out in human and other drug development-related mammal species to confirm absorption, distribution, metabolism and excretion characteristics of DCC-2618 and active metabolite DP-5439. In vivo PK studies (oral administration and intravenous injection) were carried out in rodents (mice and rats) and non-rodents (dogs and cynomolgus monkeys).

DCC-2618 presented certain oral bioavailability in different species, which proved its development potential as an oral therapeutic drug.

Exposure ($AUC_{0\text{-}24hr}$) of DCC-2618 in dogs and rats was 1.9 - 2.6 times that of DCC-2618 and metabolite DP-5439 in the mouse GIST efficacy model. Dogs and rats were given a single IV dose, and $T_{1/2}$ was equivalent in dogs (2.7 hours) and rats (2.0 hours).

Metabolite identification study indicated that all metabolites found in human were also observed in Sprague-Dawley rats and/or Beagle, indicating these specimens had correlation with toxicological studies. The main hepatocellular metabolite in all specimens was N-desmethyl metabolite (DP-5439). The study has confirmed that DP-5439 is a receptor tyrosine kinase inhibitor and remains the inhibitory activity to wild-type and KIT and PDGFRA mutations similar to drug DCC-2618. In testing of 19 single and double KIT mutants conducted in transfected Chinese Hamster Ovary Cells (CHO), DCC-2618 inhibited phosphorylation of mutant KIT; median maximum inhibition concentration (IC50) ranged 6 nM - 221 nM. Similarly, IC50 range of metabolite DP-5439 in inhibiting phosphorylation of mutant KIT was 21 nM - 191 nM.

In in vitro metabolism study, in vitro metabolism of DCC-2618 and active metabolite DP-5439 by human liver microsome was studied to confirm which human cytochrome P450 (CYP) is conducive to DCC-2618 metabolism. It is found that metabolism of DCC-2618 was dependent upon the existence of reduced nicotinamide adenine dinucleotide phosphate (NADPH). By jointly giving specifically direct or metabolism-dependent CYP inhibitors to block the metabolism of DCC-2618 in cultured human liver microsome, it was found that CYP3A4/5 was the main metabolic enzyme (ketoconazole, 63% inhibition; troleandomycin, 79% inhibition) of DCC-2618; CYP2C8 (gemfibrozil-glucuronic acid, 24% inhibition) and CYP2D6 (quinidine, 26% inhibition) were regarded as secondary metabolic enzymes. However, in recombinant human CYP enzyme products, it was also found that CYP2D6 and CYP2C8 were potent metabolic enzymes of DCC-2618. It was found that the metabolism of DP-5439 was inhibited by adding direct inhibitor ketoconazole (CYP3A4/5, 72％ inhibition), metabolism-dependent inhibitor gemfibrozil-glucuronic acid (CYP2C8, 59％ inhibition), esomeprazole (CYP2C19, 31% inhibition), paroxetine (CYP2D6, 42% inhibition),

diethyldithiocarbamate (CYP2E1, 50% inhibition) and troleandomycin (CYP3A4/5, 100% inhibition) into cultured human liver microsome. When DP-5439 and other direct or metabolism-dependent inhibitors were cultured together, inhibition rate was lower than 14%. The study indicated that CYP3A4/5 was the main metabolic enzyme of DP-5439, but CYP2C8, CYP2E1 and CYP2D6 also played an important role in the metabolism of DP-5439. In in vitro metabolism study, DCC-2618 did not significantly inhibit cytochrome P450 (CYP) 3A4, CYP1A2 or CYP2B6. IC50 of DCC-2618 in inhibiting CYP2C8, CYP2C9, CYP2C19 and CYP2D6 ranged 0.12 - 1.8 μM. There is little or no evidence that DCC-2618 has time- or metabolism-dependent inhibitory effect on any of the evaluated 7 main CYP enzymes.

Similarly, it was also found that IC50 of metabolite DP-5439 in inhibiting CYP2C8, CYP2C9, CYP2C19 and CYP2D6 ranged 0.30 - 2.0 μM. DP-5439 did not directly inhibit CYP3A4, CYP1A2 or CYP2B6. However, after incubating together with human liver microsome for 30 minutes in the presence of NADPH, it was proved that DP-5439 had metabolism-dependent (time-dependent and NADPH-dependent) inhibitory effect on CYP3A4/5-mediated testosterone 6β-hydroxylation. After preincubating, it was observed that the inhibition rate increased by 41% in the presence of 7.0 μMDP-5439. There is little or no evidence that DP-5439 has metabolism-dependent (time- and NADPH-dependent) inhibitory effect on CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP2D6. DCC-2618 and DP-5439 have potential drug interaction with other drugs metabolized dependent upon CYP2C8, CYP2C9, CYP2C19 or CYP2D6.

In the presence of 10 μM DCC-2618 or 7 μM DP-5439, organic anion transporter (OAT) OAT1 and OAT3, organic cation transporter (OCT) OCT1 and OCT2 were mildly or moderately inhibited $\leq$ 55%. Inhibition rate of DCC-2618 on OATP1B3 was 78% and that of DP-5439 on OATP1B1 was 73% (Table 2).

In vitro vesicular transportation analysis showed that both DCC-2618 and DP-5439 inhibited efflux transporter breast cancer resistance protein (BCRP), and IC50 was 0.04 μM and 1.26 μM, respectively. Although DCC -2618 is not the substrate of BVRP transporter (efflux rate [ER] 2.36), metabolite DP-5439 presented significant substrate activity (ER 85.0), indicating the possibility of drug-metabolite interaction. DCC-2618 was the substance inducing interaction (BCRP IC50 was 0.04 μM) and metabolite DP-5439 may be a substance influenced by DDI (BCRP ER 85.0). DCC-2618 may have drug interaction with substrate or inhibitor of other BCRP efflux transporters.

DCC-2618 and DP-5439 had a moderate to weak inhibitory effect on multidrug resistance efflux transporter 1 (MDR1), and IC50 was 1.95 μM and > 7 μM, respectively. Although DCC-2618 is a moderate substrate of MDR1 transporter (ER 12.9), metabolite DP-5439 exhibited significant substrate activity (ER 72.4), indicating that the possibility of drug-metabolite interaction was low to moderate; DCC-2618 was likely to be the substance inducing interaction (MDR1 IC50 1.95 μM), and metabolite DP -5439 may be a substance

influenced by DDI (MDR1 ER 72.4).

Table 2 Interaction between DCC-2618, its metabolite DP-5439 and transporters

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

BCRP = breast cancer resistance protein; BSEP = bile salt export pump; ER = efflux rate; IC50 = median maximum inhibition concentration; MDR1 = multidrug resistance protein 1; NT = not tested; OAT = organic anion transporter; OATP = organic anion transporting polypeptide; OCT = organic cation transporter

a. In the study of MDCKII cells expressing BCRP transporter, ER of BCRP transporter was 85.0. Because MDCKII cells also express other background transporters, study personnel also studied the characteristics of BCRP substrate of DP-5439 in vesicles only expressing BCRP transporter. In the BCRP vesicle study, DP-5439 did not show substrate activity. However, it was proved in a qualitative study in LLC-PK1 cells expressing and controlling human BCRP that DP-5439 was a substrate of BCRP and efflux rate was 41.8.

1.2.1.3 Toxicology

In vivo and in vitro toxicological characteristics of DCC-2618 were assessed in bacterial mutagenicity analysis in nude mice, Sprague-Dawley rats and Beagle. Under the maximum test concentration of 3000 μg/plate (precipitation concentration), regardless of metabolic activation, bacterial mutagenicity was not observed.

In a critical study in rats, oral doses of DCC-2618 included: 0, 15, 60 and 300 mg/kg/day, and there was a 4-week recovery period after administration. There were no drug-related deaths or adverse events in this study. Incidence of hair thinning at 300 mg/kg/day was high. Weight and food consumption decrease was observed in animals processed with DCC-2618. In the recovery period, weight and food consumption reversed and it did not have any impact on the overall status of animals. Several minor clinical pathological findings were observed on Day 29. These changes were not mild, showed no microscopic correlation, presented reversibility after the recovery period, and were not regarded to be adverse. DCC-2618-related lung weight increase (15 - 33%) was observed in male rats administered at a dose of 300

mg/kg/day and female rats administered at a dose ≥15 mg/kg/day. In the recovery period, there was no related microscopic change and lung weight increase was partially reversed. Microscopic changes were limited to forestomach (nonglandular stomach) of rats administered at doses ≥ 60 mg/kg/day (diffuse hyperplasia/hyperkeratoses) and were partially reversed in the recovery period. These changes were unrelated to human because human do not have the anatomical feature. On the basis of these results, 300 mg/kg/day is the no-observed-adverse-effect level (NOAEL) after 4 weeks of administration

in a critical study of 4-week oral administration at 0, 7, 20 and 75 mg/kg/day in Beagle dogs complying with the GLP. There was a 4-week recovery period after administration. Since DCC-2618-related adverse events were observed, the drug was withheld in several animals in 20 and 75 mg/kg/day dose groups at weeks 2 and 3. Due to DCC-2618-related adverse events, 3 male rats in 75 mg/kg/day dose group were executed on Day 13; 4 rats (2 males and 2 females) in 20 mg/kg/day group and 3 rats (females) in 75 mg/kg/day dose group were executed at Week 4. Adverse events in these animals included foot erythema, erythema in ears, mouth, periorbital area and on ventral chest, and head hair thinning. Some dogs also manifested dry and flaky skin, otitis, external ear canal erythema, excessive salivation, vomiting and shapeless/liquid feces. In dogs of the 7 mg/kg/day dose group, the severity of skin changes was mild and was not judged as adverse. In the recovery period, skin damage in the 20 and 75 mg/kg/day dose groups partially or completely resolved. Body weight of male rats in 20 or 75 mg/kg/day dose groups decreased. Body weight of animals in the 7 mg/kg/day dose group changed slightly, which was not regarded as adverse. Change in blood pressure or ECG intervals was not observed in any DCC-2618 dose groups. In animals of dose ≥ 20 mg/kg/day group, mild hematological, clinical biochemical and/or coagulation function abnormalities were observed and there was evidence that all changes were reversed after the recovery period. In animals handled with DCC-2618, troponin I was not influenced by drug. In animals of dose ≥20 mg/kg/day group, such as hyperkeratoses, microscopic changes of sparse cytoplasm of liver cells, consistent with glycogen increased, lymphocytes decreased in lymphoid tissues and one case of intraepithelial pustule were observed. The only microscopic finding related to the test product in animals in the recovery period was minimum cytoplasm sparsity in hepatocytes of some animals in the 75 mg/kg/day group, indicating that the abnormality was only partially recovered.

On the basis of these results, NOAEL in Beagle dogs 4 weeks after administration was 7 mg/kg/day and the dose was also considered to be the highest non-severely toxic dose.

1.3 Investigational drug

DCC-2618 is a new orally administered KIT kinase and PDGFRA kinase inhibitor developed by Deciphera Pharmaceuticals, LLC using its special kinase switch control inhibitor technological platform. DCC-2618 can comprehensively and potently inhibit extensive primary and secondary KIT and PDGFRA kinase mutants, including primary exons 9 and 11

mutations, secondary exons 13 and 14 mutations in KIT ATP-binding/transformation pocket, and primary and secondary exons 17 and 18 mutations in activation loop conformation-control switch region. DCC-2618 can also inhibit primary exon 18 D842V mutations in PDGFRA conformation-control switch region and assist in inhibiting exon 12 mutation in switch region. DCC-2618, as an enhanced type II kinase inhibitor, penetrates embedded KIT/PDGFRA switch pocket by binding to extensively inhibit KIT/PDGFRA mutants.

1.3.1 Clinical summary

As of the data cutoff 10 August 2019 of Investigator's Brochure Version 5.0, Deciphera had finished two clinical studies and four clinical studies are on-going. The completed studies include two phase 1 clinical pharmacological studies in healthy subjects. On-going studies include a phase 1 study in patients with advanced malignant tumors (DCC-2618-01-001), a phase 1 study in patients with hepatic impairment (DCC- 2618-01-004), and two phase 3 studies in GIST patients (INVICTUS, DCC-2618-03-001; INTRIGUE, DCC-2618-03-002).

Study DCC-2618-01-001 is a study first conducted in human being and a open-label, ascending dose study in patients with advanced malignant tumors with molecular evidence. The primary objective of this study is to assess the safety, tolerability, preliminary efficacy, PK and PD effect of DCC-2618. The study consists of two parts: (1) Dose escalation phase; (2) Extension stage.

In the dose escalation period, the safety of DCC-2618 administered orally twice daily (BID) based on a 28-day cycle was evaluated according to 3+3 dose escalation rules as pharmacologically guided until confirming the maximum tolerated dose or recommended expansion dose. Plasma half-life of active metabolite may be very long (30 - 60 hours), administration daily is supported. Therefore, dosing regimen of DCC-2618 administered orally once daily (QD) is also evaluated.

In the dose escalation period, 9 dose levels were evaluated: 20 mg BID, 30 mg BID, 50 mg BID, 100 mg BID, 150 mg BID, 200 mg BID, 100 mg QD, 150 mg QD and 250 mg QD. In the dose escalation period, three cases of dose-limiting toxicity occurred: one patient in 100 mg BID group and 200 mg BID group respectively experienced asymptomatic grade 3 lipase increased; one patient in the 150 mg QD group experienced asymptomatic grade 4 creatine phosphokinase (CPK) increased. As specified in the protocol, the above lipase increased and creatine phosphokinase (CPK) increased are dose-limiting toxicities. Because patients did not have related symptoms, the investigator judged that they were not clinically significant.

The MTD was not reached during the dose escalation phase. According to data of safety, tolerability, PK and efficacy observed in the dose escalation phase, it is suggested that the recommended phase 2 dose (RP2D) be 150 mg QD. At present, the 150 mg QD group in the dose expansion period is recruiting patients to further evaluate safety, PK, PD and inhibitory activity on multiple tumors with gene changes (DCC-2618 target). The expansion study will

recruit several groups of patients who have the following diseases: GIST, SM and other malignant hematological tumors, malignant glioma, other solid tumors, melanoma, soft tissue sarcoma, germ cell neoplasm, penis carcinoma, non-small cell lung cancer (NSCLC), solid tumors with renal insufficiency carrying KIT or PDGFRA mutations.

As of 10 August 2019, 256 patients were enrolled to study DCC-2618-01-001 and received at least one dose of ripretinib. Therefore, these patients were included to safety population. 68 out of 256 patients (26.6%) are still taking part in the study and continue receiving the study treatment. Patient recruitment has stopped for the dose escalation stage of the study, whereas it is underway for the dose expansion stage.

Study DCC-2618-01-004 is an on-going, phase 1, open-label study to assess PK, safety and tolerability profile of ripretinib in patients with hepatic image defined based on Child Pugh classification compared with healthy subjects. The study plans to enroll about 40 subjects (a maximum of 24 patients with hepatic damage and a maximum of 16 matching healthy subjects). The study is enrolling subjects and clinical data was not available on data cutoff (10 August 2019).

DCC-2618-03-001 (Invictus) is a phase 3, double-blind, placebo-controlled, randomized (at a 2:1 ratio between the DCC-2618 group and the placebo group), multinational study conducted in patients with advanced gastrointestinal stromal tumors (GIST) who have received ≥ 3 prior treatments (including designated imatinib, sunitinib and regorafenib). The primary objective of this study is to evaluate the efficacy in the DCC-2618 group and the placebo group (independent radiology review based progression-free survival [PFS]). As of 31 May 2019, 114 patients were exposed to ripretinib in study INVICTUS. Eighty-five patients receive randomized allocation and treatment with ripretinib at 150 mg QD. Forty-four patients were randomized to receive placebo therapy (1 patient received randomized allocation but didn't receive treatment; therefore, only 43 patients received placebo therapy). Another 29 patients receiving placebo have crossly given ripretinib treatment after disease progression based on IRR was determined.

Study DCC-2618-03-002 (Intrigue) is a phase 3, interventional, randomized, multicenter, open-label study aiming to compare the efficacy of DCC-2618 and sunitinib in patients with advanced GIST after treatment with imatinib. It is planned that about 358 patients will be randomly assigned (1:1) into the test group and control group. About 115 study sites worldwide will take part in the study and the primary endpoint is IRR-assessed PFS. Recruitment of this study is underway. As of 10 August 2019, 38 patients had been enrolled.

Specific information of two completed clinical studies can refer to relevant sections of Investigator's Brochure Version 5.0.

1.3.1.1 Clinical Safety

1.3.1.1.1 Study DCC-2618-01-001

The study is the first study of DCC-2618 in human subjects. As of August 10, 2018, a total of 256 patients were exposed to the initially assigned dose of DCC-2618 in study DCC-26180-1-001 (see Table 3), including 184 GIST patients (81%), 24 patients with brain carcinoma (11%), 5 patients with melanoma (2%), 4 SM patients (1.8%) and 10 patients with other solid tumors (4%). GIST patients enrolled in DCC-2618-01-001 have received 1 to 7 prior treatments.

Table 3 Patients exposed to DCC-2618 in study DCC-2618-01-001

	Assigned dose									
Dose	**20 mg BID n (%)**	**30 mg BID n (%)**	**50 mg BID n (%)**	**100 mg QD n (%)**	**150 mg QD n (%)**	**200 mg QD n (%)**	**100 mg QD n (%)**	**150 mg QD n (%)**	**250 mg QD n (%)**	**Total N**
Number of Subjects	4 (1.6)	4 (1.6)	11 (4.3)	12 (4.7)	7 (2.7)	7 (2.7)	6 (2.3)	199 (77.7)	6 (2.3)	256

BID = twice daily; QD = once daily; N = total number of patients.

Data cutoff date: 10 August 2019

Regardless of the correlation with the investigational drug and dose level received by the reported case, TEAE (all levels) with an incidence ≥ 25% included: lassitude (50.4%), alopecia (46.5%), nausea (37.1%), myalgia (34.4%), constipation (32.4%), appetite decreased (31.3%), palmar-plantar erythrodysesthesia syndrome (30.9%), diarrhea (28.1%) and lipase increased (27.3%).

As of 10 August 2019, of the 256 patients:

Ninety-seven (39.2%) experienced at least one SAE during the study and most of which were not related to the investigational drug at the investigator's discretion. According to the preferred term, the most common SAEs (≥ 5 cases) included: death (n = 16, 6.3%), abdominal pain (n = 15, 5.9%), cancer surgery (n = 9, 3.5%), breathing difficult (n = 8, 3.1%), anemia and septicemia (n = 7 for each, 2.7%), GIST and urinary tract infection (n = 5 for each, 2.0%).

Thirty-six (14.1%) patients experienced at least one SAE related to the investigational drug at the investigator's discretion. Thirty-three patients experienced ≥ grade 3 SAE related to the investigational drug at the investigator's discretion, including: one case (0.4%) of grade 5 myocardial infarction; one case (0.4%) of each of grade 4 blood creatine phosphokinase (CPK) increased, hyponatremia, lipase increased and pancreatitis; grade 3 SAEs included two cases 0.8% of each of blood bilirubin increased and pancreatitis; one case (0.4%) of each of dissection of aorta, deep vein thrombosis, heart failure, myocardiosis, cognitive disorder, diarrhea, diastolic dysfunction, ECG abnormality, enterocolitis, flushing, gastrointestinal tract bleed, hypertension, hypertriglyceridemia, hypotension, infection, lipase increased, myasthenia, non-cardiac chest pain, pain in extremity, plasma cell myeloma, pulmonary embolism, pyramidal tract syndrome, Syndrome Stevens-Johnson (SJS), and supraventricular

tachycardia (SVT).

1.3.1.1.2 Study DCC-2618-03-001

As of 31 May 2019, the most common TEAEs (≥ 25%) in patients who are randomized to ripretinib group in the double-blind stage included: alopecia (51.8%; placebo 4.7%), fatigue (42.4%; placebo 23.3%), nausea (38.8%; placebo 11.6%), abdominal pain (36.5%; placebo 30.2%), constipation (34.1%; placebo 18.6%), myalgia (31.8%; placebo 11.6%), diarrhea (28.2%; placebo 14.0%) and appetite decreased (27.1%; placebo 20.9%).

As of 31 May 2019, 26/85 patients (30.6%) and 19/43 patients (44.2%) in the ripretinib group and placebo group in the double-blind stage reported at least one case of SAE during treatment. Eight patients (9.4%) and three patients (7.0%) experienced at least one case of SAE related to the investigational drug. In the double-blind stage, SAEs (n ≥ 2) in the ripretinib (150 mg QD) treatment group included: abdominal pain (n = 4, 4.7%), anemia and death (n = 3 for each, 3.5%), nausea and vomiting (n = 2 for each, 2.4%).

As of 31 May 2019, in the double-blind stage or long-term follow-up, a total of 25 patients died (12 patients received ripretinib treatment and 13 patients received placebo treatment). Most of the deaths were caused by disease progression (11 patients in each of ripretinib group and placebo group). Five patients (5.9%) in the ripretinib group and 10 patients (23.3%) in the placebo group died during the study treatment or within 30 days after the last dose.

As of 31 May 2019, 6 patients (7.1%) in the ripretinib group and 1 patient (2.3%) in the placebo group reported AESI in the double-blind stage.

Please refer to the Investigator's Brochure Version 5.0 for more detailed safety information.

1.3.1.2 Clinical Pharmacokinetics and Pharmacodynamics

It was confirmed in non-clinical study that DP-5439 as an active metabolite had a similar activity with the original drug DCC-2618. Long half-life of metabolite (30 - 60 hours) supports the dosing regimen on a once daily basis. Food influence study showed that DCC-2618 taken with food did not have influence on absorption.

The mean $T_{1/2}$ of DCC-2618 ranged from 8.04 - 11.1 hours and was evaluated only in the single dose group. Detected active metabolite DP-5439 was about 50 - 200% of the original drug (DCC-2618). Half-life of DP-5439 was not calculated.

Study personnel compared the rate of accumulation of DCC-2618 and DP-5439 on C1D15 and C1D1. For QD dosing regimen, in terms of C_{max} and AUC_{0-12}, the rate of accumulation of DCC-2618 was 0.725 - 1.47 and 0.707 - 1.69, respectively. In terms of C_{max} and AUC_{0-12}, the rate of accumulation of DP-5439 was 0.968 - 3.46 and 1.32 - 4.88, respectively.

From 100 mg QD to 250 mg QD, exposure of DCC-2618 and DP-5439 was likely to be proportional to the dose. Because pharmacokinetices of the drug changes rapidly and sample size for each dose level was small, formal PK linear correlation assessment was not carried

out.

For GIST patients who have received multiple prior treatments, DCC-2618 could rapidly eliminate plasma cfDNA with broad-spectrum KIT mutations. Overall, total plasma concentration (C_{max}) in the 100 mg BID group on C1D15 was very high, more than 5 μM (3,000 ng/mL); the observed mean exposure was far more than the target plasma level, including exposure level for KIT mutations (V654A and T670I) most insensitive to DCC-2618.

At baseline, all GIST patients received next generation plasma free DNA sequencing (cfDNA) once every 2 cycles during the study. Mutations were tested and quantified with Guardant 360 v2.9 or v2.10. Amino acid mutation only in KIT and PDGFRA was regarded as resistance-conferring mutations. Free DNA was not detected in all patients. According to the preliminary data, 19 unique gene mutations were observed in GIST patients with 11/29 KIT mutations. In exons 9. 11, 13, 14, 17 and 18, a total of 43 mutations were detected in KIT gene. Of 4 enrolled patients with PDGFRA D842V-mutation (confirmed according to previous archived results of patients), PDGFRA D842V-mutation was detected only in the sample of one patient.

1.3.1.3 Clinical Efficacy

1.3.1.3.1 Study DCC-2618-01-001

As of 10 August 2019, study personnel had obtained efficacy data of 178 evaluable patients (measured according to Response Evaluation Criteria In Solid Tumours [RECIST] Version 1.1), including 142 GIST patients who received 150 mg QD dose. Study personnel analyzed PFS data according to the number of treatment. Data indicated that the number of patients who took DCC-2618 as second-, third-, fourth-line treatment and above was 31, 28, 46 and 83, respectively; confirmed ORR was 19.4%, 14.3%, 10.9% and 7.2%, respectively; mPFS was 46.4 weeks, 36.3 weeks, 24.1 weeks, and 23.9 weeks respectively.

1.3.1.3.2 Study DCC-2618-03-001

Only efficacy data (n = 129) in the double-blind stage as of 31 May 2019 are listed. The median (95% CI) of PFS in the ripretinib group was 27.6 (20.0, 29.9) weeks and that in the placebo group was 4.1 (4.0, 7.3) weeks. Risk of disease progression or death in patients who received ripretinib treatment decreased by 85%, showing statistically significant difference with the placebo group (HR 0.15; stratified log-rank test $P < 0.0001$). At week 26, 51.0% of patients receiving ripretinib treatment and 3.2% of patients receiving placebo didn't have disease progression (estimated PFS rate).

Confirmed ORR was 9.4% in the ripretinib group and 0% in the placebo group ($P = 0.0504$, Fisher's exact test); however, statistical significance was not reached.

OS results of the placebo group included OS data of patients in the placebo group who

received ripretinib treatment crossly after IRR-assessed disease progression. During the final analysis, 29 patients (65.9%) in the placebo group were subject to crossover treatment in the treatment group and received at least one dose of ripretinib. Of 85 patients in the ripretinib group, 26 patients (30.6%) experienced OS events and 59 patients (69.4%) were censored. Of 44 patients in the placebo group, 26 patients (59.1%) experienced OS events and 18 patients (40.9%) were censored.

The median (95% CI) of OS in the ripretinib group was 65.6 (53.6, 65.6) weeks and that in the placebo group was 28.6 (17.9, 50.4) weeks. Compared with those in placebo group, the risk of death in patients receiving ripretinib decreased by 64% (HR 0.36; stratified log-rank test P = 0.0004).

1.4 Study rationale

1.4.1 Rationale for the Study

There is no standard treatment for advanced or unresectable GIST patients after failure of imatinib, sunitinib and regorafenib. Secondary KIT mutations causing drug resistance are highly heterogeneous. Patients who failed prior treatments may have multiple acquired resistance-conferring mutations, and it is difficult to carry out clinical study in the population. There are very limited data that support the resuming of drugs which were ineffective in the past. A Korean, single-center, randomized, placebo-controlled study (RIGHT trial) showed that benefit from resuming imatinib (mPFS = 1.8 months) was less than that from using placebo (mPFS = 0.9 month)[28]. However, subgroup analysis in the study showed that accompanying symptoms of patients were not relieved[29], and health-related quality of life was assessed with EORTC QLQ-C30 questionnaire. RIGHT trial excluded patients who obtained limited benefit from initial imatinib treatment (defined as PFS ≤ 6 months). Therefore, patients who succeeded in initial imatinib treatment are inclined to be enrolled. Resuming imatinib is not the approved standard treatment worldwide. Many doctors choose imatinib as second-line treatment according to patients' medical history.

DCC-2618 is a pan KIT and PDGFRA inhibitor. In phase 1 study DCC-2618-01-001, all patients received adequate prior treatment and were resistant to TKI. DCC-2618 presented an encouraging anti-tumor effect (see Section 1.3.2 Clinical Summary for specific data). Phase 1 study results were consistent with non-clinical study results, indicating that DCC-2618 was effective on all tested KIT and PDGFRA mutations. For GIST patients who have received adequate prior treatments and are resistant to TKI, DCC-2618 can significantly decrease allete frequency with KIT exons 13, 14, 17 and 18 and PDGFRA D842V resistance-conferring mutations. The above observed clinical efficacy and decreased allele frequency support that DCC-2618 can effectively treat GIST patients who failed prior treatments (7 at most).

In view of the above basis, Deciphera carried out a phase 3, double-blind, placebo-controlled,

randomized (at a 2:1 ratio between the DCC-2618 group and the placebo group), multinational study (Invictus) in patients with advanced gastrointestinal stromal tumors (GIST) who have received ≥ 3 prior treatments (including imatinib, sunitinib and regorafenib). Deciphera had submitted new drug application (NDA) to FDA in December 2019 based on data of studies DCC-2618-01-001 and DCC-2618-03-001 and FDA approval of marketing in US was obtained on 15 May 2020 for the treatment of four-line and higher advanced GIST patients (see Section 1.3.2 Clinical Summary for specific data).

This study is a phase 2 bridge study in Chinese population. Considering that GIST epidemiology, pathogenesis, and clinical treatment practice are highly similar in Chinese and western populations, the study adopted single-arm design. Study population was consistent with the population in study Invictus, that is, advanced GIST patients who have received ≥ 3 prior treatments (including designated imatinib, sunitinib and regorafenib). For patients who do not have standard treatment after failure of imatinib, sunitinib and regorafenib, their unsatisfied clinical demand was similar and comparable to study Invictus. This study evaluated the efficacy and safety of DCC-2618 and observed pharmacokinetic characteristics of DCC-2618 in Chinese GIST patients. If data of DCC-2618 in Chinese patients who received the same number of treatments were consistent with data obtained by study Invictus, and pharmacokinetic characteristics of DCC-2618 were consistent with that in foreign patients, it is supported that DCC-2618 can be used in this indication in China.

1.4.2 Rationale for Dose, Dosing Regimen, and Treatment Period

1.4.2.1 Dose Selection

This section describes the scientific basis for selecting the dosing regimen of 150 mg QD of DCC-2618 for advanced GIST patients in the phase 3 study. Dose selection is based on non-clinical pharmacology, clinical PK evaluation and PD results in phase 1 study (as of 1 June 2017).

1.4.2.1.1 In Vitro Pharmacology

In vitro pharmacological study proved that DCC-2618 and its metabolite DP-5439 can potently inhibit wild-type, carcinogenic KIT mutants, and IC50 was 3 - 20 nM. See Table 5. The following table shows the available data of KIT inhibitors including imatinib, sunitinib and regorafenib for reference. Imatinib, sunitinib, regorafenib and DCC-2618 generated active metabolites. The following doses are mainly based on pharmacological characteristics of drug prototype compound.

Table 4 In vitro inhibitory effect on recombinant KIT and KIT mutants

	wt KIT	KIT V654A Exon 13	KIT T670I Exon 14	KIT D816H Exon 17	KIT D816V Exon 17	KIT ΔV559-V560/D816V Exon 11&17
IC_{50} (nM)						
Imatinib	34	606	3500	>10.000	>10.000	>10.000
Sunitinib	6	3	9	1800	2,200	770
Regorafenib	3	28	7	120	>3,300	>3,300
DCC-2618	3	11	8	3	8	9
DP-5439	6	15	19	20	11	n.d

IC_{50} = median maximum inhibition concentration; n.d. = not determined; wt = wild type

It is reported that unbound fraction (fu) of imatinib and sunitinib was same (5%), but in vitro effect of sunitinib (wide-type) was 6 times that of imatinib. For the treatment of GIST, daily dose of sunitinib (125 μmol, 50 mg) was 6.5 times lower than that of imatinib (810 μmol, 400 mg) (based on molar dose ratio). It is reported that fu of regorafenib was 0.5%, 10 times lower than that of sunitinib, but in vitro effect was 2 times that of sunitinib. However, for the treatment of GIST, daily dose (331 μmol, 160 mg) of regorafenib was only 2.6 times that of sunitinib (based on molar dose ratio). This may be cause it has an inhibitory effect on more KIT mutants.

In vitro fu of DCC-2618 to albumin and alpha-1-acid glycoprotein was 0.2% and 0.6-1.4%, respectively, closer to that of regorafenib (fu = 0.5%) than that of imatinib or regorafenib (fu = 5%). Molecular weight of DCC-2618 (510.4 Dalton) is slightly higher than that of regorafenib (482.8 Dalton). Therefore, for the treatment of GIST, estimated daily dose of DCC-2618 (294 μmol, 150 mg) was close to that of regorafenib (331 μmol, 16 0 mg). However, because inhibitory effect of DCC-2618 was stronger on KIT mutant exons 17 and 11, its optimal dose may be lower.

1.4.2.1.2 In Vivo Pharmacology

In exon 11 mutant KIT GIST T1 cell line xenograft mouse model, within 8 hours after single oral dose of DCC-2618 at 50 mg/kg, inhibition rate of KIT signal transduction reached 69 - 88%; within 12 hours after administration, the inhibition rate remained 40%. After orgal administration to the GIST T1 xenograft model, 50 mg/kg DCC-2618 could significantly inhibit tumor growth, with an inhibition rate reaching 90%. In imatinib-resistant GIST patient-derived xenograft (PDX) model, 100 mg/kg QD or 50 mg/kg BID DCC-2618 could completely stop tumor growth. In Kasumi-1 AML xenograft model expressing primary exon 17 KIT mutation (N822KKIT), DCC-2618 100 mg/kg and 50 mg/kg showed stable efficacy, while imatinib 50 mg/kg BID was ineffective.

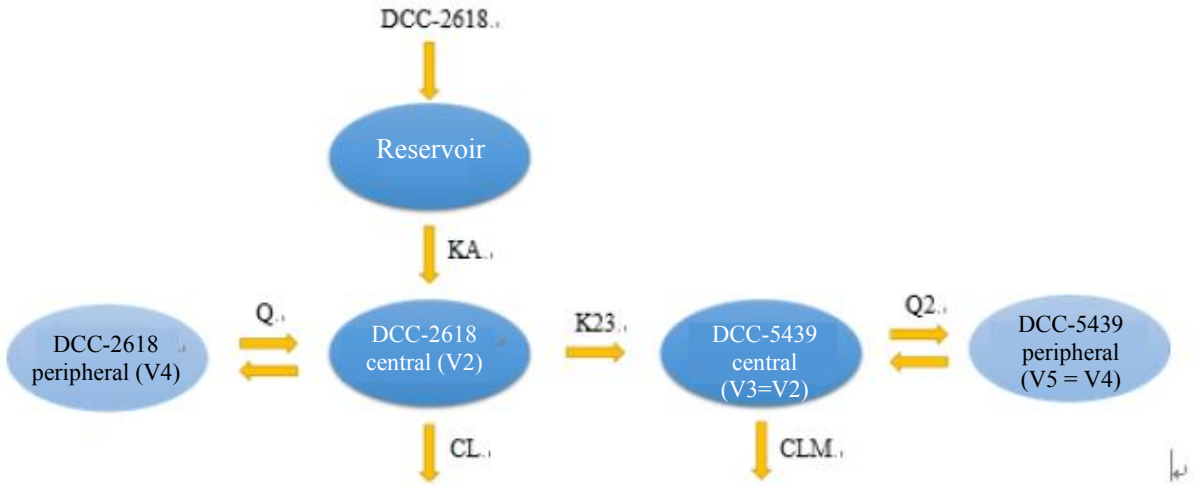
According to in vivo pharmacological study, under the steady state, in terms of combining 24-hour area under the time-concentration curve ($AUC_{0\text{-}24hr}$) of DCC-2618 and DP-5439, it

was confirmed that target PK exposure for suppressing tumor growth was 10,000 ng*h/mL.

1.4.2.1.3 Clinical Pharmacokinetic Evaluation

Group PK analysis was carried out by collecting data of patients with advanced malignant tumors administered BID and QD from the ongoing phase 1 study (study DCC-2618-01-001; data cutoff 1 June 2017). Please see Figure 3 for model structure. PK characteristics of DCC-2618 and DP-5439 were described through two-compartment model. Reservoir means the gastrointestinal tract with oral DCC-2618. KA is first-order absorption rate constant of DCC-2618; K23 is the first-order rate constant of DCC-2618 metabolizing its active metabolite DP-5439 through CYP3A4/5. CL and CLM represent DCC-2618 clearance and DP-5439 clearance through other enzyme pathways, respectively. It is assumed that central and peripheral volume of distribution of DP-5349 are similar to those of DCC-2618 to avoid over-parametrization.

Figure 3 Drug pharmacokinetic model of DCC-2618 and DP-5439 in patients with advanced malignant tumors



Although there were a few patients in each group, group analysis of combining data of BID and QD groups (total number = 44) showed PK of DCC-2618 and DP-5439 in cancer patients was dose proportionally. See Table 5 for steady-state PK exposure predicted by the model.

Table 5 Typical steady-state exposure of DCC-2618 and DP-5439 predicted by models in patients with advanced malignant tumors

Dose interval	Dose	Analyte	C_{trough} (ng/mL)	C_{max} (ng/mL)	AUC_{24h} (ngh/mL)
BID	20	DCC-2618	131	171	3736
		DP-5439	207	225	5211
		Combination	338	396	8947
	30	DCC-2618	197	257	5603
		DP-5439	310	337	7816

Dose interval	Dose	Analyte	C_{trough} (ng/mL)	C_{max} (ng/mL)	AUC_{24h} (ngh/mL)
		联合	507	594	13419
	50	DCC-2618	328	428	9339
		DP-5439	517	561	13027
		Combination	845	989	22366
	100	DCC-2618	655	857	18678
		DP-5439	1034	1123	26054
		Combination	1689	1980	44732
	150	DCC-2618	983	1285	28017
		DP-5439	1551	1684	39081
		Combination	2534	2969	67098
	200	DCC-2618	1311	1714	37356
		DP-5439	2068	2246	52108
		Combination	3379	3960	89464
QD	100	DCC-2618	249	510	9348
		DP-5439	457	609	13041
		Combination	706	1119	22389
	150	DCC-2618	373	766	14021
		DP-5439	685	914	19562
		Combination	1058	1680	33583

C_{trough} = concentration at the end of dose interval; C_{max} = maximum concentration; AUC_{24h} = 24-hour area under the time-concentration curve; BID = twice daily; QD = once daily

Group PK analysis indicated after administering 30 - 200 mg BID or 100 - 150 mg QD DCC-2618 to typical cancer patients, combining stable PK exposure ($AUC_{0\text{-}24hr}$) of DCC-2618 and DP-5439 was more than 10,000 ng*h/mL efficacy threshold confirmed by xenograft mice institution. However, PK of DCC-2618 and DP-5439 observed in patients was highly variant.

One hundred studies were simulated with group PK model and each study contained 100 patients; the proportion of subjects reaching 10,000 ng*h/mL efficacy threshold was evaluated. Results showed that at a dose of 150 mg QD (estimated by comparing in vitro pharmacology), it was estimated that PK exposure of 93.6% of patients maintained over 10,000 ng*h/mL. When it was simulated with 100 mg QD, it was estimated that 87.9% of patients would reach the efficacy threshold.

1.4.2.1.4 Summary

It is recommended oral DCC-2618 150 mg QD be taken the optimal dose regimen for the treatment of GIST for the following reasons:

- Comparison of in vitro pharmacological properties between DCC-2618 and three approved target therapeutic drugs for the treatment of GIST showed that when treating GIST patients, effectively daily dose of DCC-2618 was ≤ 160 mg.

- In vivo pharmacological study in xenograft mouse model indicated that target combination PK exposure (AUC0-24hr = 10,000 ng*h/mL) of DCC-2618 and DP-5439 could inhibit tumor growth. At the dose of oral 150 mg daily, it was estimated that exposure of 93.6% of patients maintained over the threshold.
- Both in vitro and in vivo pharmacological data showed that 150 mg QD was an effective dose.
- Safety data collected from phase 1 study support that the dose of 150 mg QD is the tolerable dose.

Other considerations are as follows:

- Compared with BID dosing regimen for reaching the effective exposure, administration once daily is more convenient and increases patient compliance. Therefore, 150 mg QD is better than 150 mg BID.
- In view of significant individual difference in PK, doses lower than 150 mg may result in exposure of more patients lower than the effective exposure threshold.
- For most patients (87.9%), it is estimated that a dose of 100 mg QD can reach the effective exposure threshold. If individual patient is unable to tolerate 150 mg QD, the dose can be reduced to 100 mg QD without influencing the efficacy.
- Further PK-efficacy and PD-safety assessment proved that the optimal dosing regimen of DCC-2618 in GIST patients was 150 mg QD.

1.4.2.2 Dose escalation after PD

Dose escalation of other TKIs (imatinib) has become a treatment choice for patients with primary and secondary drug resistance to standard dose of imatinib.

On the basis of group PK model simulation, by using 150 mg QD regimen, it is estimated that about 93% of patients reach effective exposure threshold. In view of significant individual difference in PK, doses lower than 150 mg may result in exposure of more patients lower than the effective exposure threshold. Moreover, efficacy may be further improved progressively at higher doses.

The sponsor recognizes the challenge of dose optimization and well monitored dose increase after independent radiology review-based disease progression to prevent that dose increase is effective but patients can’t tolerate it.

Exploratory exposure of dose increase after independent radiology review-based disease progression is allowed in individual patient - results comparison, and it can provide important information for comprehensive safety and efficacy analysis.

2 Study objectives

2.1 Primary Objectives

- To evaluate the progress free survival (PFS) of DCC-2618 in patients with advanced gastrointestinal stromal tumors who have progressed with prior anticancer therapies based on independent radiologic review.

2.2 Secondary objective

2.2.1 Key secondary objective

- To evaluate the objective response rate (ORR) of DCC-2618 in patients with advanced gastrointestinal stromal tumors who have progressed on prior anticancer therapies based on independent radiologic review.

2.2.2 Other secondary objectives

- To evaluate overall survival (OS) in patients with advanced gastrointestinal stromal tumors treated with DCC-2618.
- To evaluate the pharmacokinetic (PK) profile of DCC-2618 in patients with advanced gastrointestinal stromal tumors who have progressed on prior anticancer therapies.
- To evaluate the safety of DCC-2618 in patients with advanced gastrointestinal stromal tumors who have progressed on prior anticancer therapies.

2.3 Exploratory objective

- To evaluate the efficacy of DCC-2618 in the patients when the dosage is increased to 150 mg BID.

3 Study design

As mentioned above, global clinical development project of DCC-2618 has comprehensively studied the efficacy, safety and pharmacokinetics of the drug. DCC-2618 presented a good efficacy, safety, tolerability and pharmacokinetic characteristics in the patient population most of whom were western patients. The study is carried out to further confirm the efficacy, safety and pharmacokinetic characteristics of DCC-2618 in Chinese advanced GIST patients who failed standard treatment,

3.1 Overview of Study Design

This study is a multicenter phase 2, single-arm open-label study of DCC-2618 to assess efficacy, safety, and pharmacokinetics in patients with advanced gastrointestinal stromal tumors who have progressed on prior anticancer therapies.

This study targets at the patients with advanced gastrointestinal stromal tumors who have progressed on prior anticancer therapies. It is planned to enroll about 35 subjects in total.

Prior anticancer therapies must include imatinib, sunitinib, and one or two other drugs, and the number of patients who have previously received treatment with ≥ fourth-line drugs should be 40% or less.

In this study, PFS based on independent radiologic review using RECIST v1.1-GIST Specific Standard is used as the primary efficacy measure for tumor efficacy assessment.

After being fully informed, signing the informed consent forms and passing the screening, the subjects will receive DCC-2618 (150 mg, QD) continuously until the occurrence of an event for treatment termination as specified in the protocol, 28 days as a treatment cycle, followed by a safety follow-up period until 30 days after the termination of study treatment.

During the study period, the subjects will be subject to visits as scheduled in the protocol. On the day of the scheduled visit as per the protocol, the subjects should bring the drug to the study site, where they will complete all the pre-dose examinations, and take the drug of the day after being suitable to continue the administration, in the discretion of the investigator. In the first four cycles (inclusive), an radiographic examination will be performed within ±7 days of each cycle and tumor efficacy will be assessed according to RECIST v1.1-GIST Specific Standard. After that, it should be performed within ±7 days every two c ycles.

If the subject discontinues treatment for reasons other than progressive disease, death, withdrawal of informed consent and loss to follow-up, the subject should receive radiographic examination for tumor assessment by independent radiologic review (IRR) after treatment withdrawal according to the frequency consistent with that during the study until presence of disease progression meeting "RECIST v1.1-GIST Specific Standard" or until starting of new anti-tumor therapy.

Based on independent radiologic review, if a subject has a radiologically confirmed progression disease (PD), the subject can choose:

- To continue DCC-2618, at an increased dose of 150 mg BID, until the occurrence of an event for treatment termination as specified in the protocol; in the case of the efficacy evaluation for such patient, the lesion diameter before the increase of dosage (but not screening period) should be taken as the baseline value.
- To continue DCC-2618 at a dose of 150 mg QD, until the occurrence of an event for treatment termination as specified in the protocol, if the subject can benefit from the treatment with DCC-2618, but cannot tolerate the increase of dosage, after being fully assessed by the investigator;
- To terminate the treatment with DCC-2618.

After subjects are enrolled into the study, PK blood samples will be collected according to the time specified in the protocol.

After PK sampling, the subjects can continue the treatment with DCC-2618, safety visits and

efficacy evaluation, until the occurrence of an event for treatment termination as specified in the protocol.

Treatment suspension or dosage reduction or treatment withdrawal is allowed at any time during the study for subjects with an intolerant toxicity reaction.

3.2 Number of subjects

The study will enroll about 35 subjects (see section “Statistical Analysis) and carried out at about 10 study sites in China.

3.3 Study duration

The study will be terminated when the last subject has been enrolled for 2 years or after the last visit of the last subject or on the sponsor's decision, whichever is the first.

For patients still taking investigational drug after the clinical trial database has been closed, if the investigator thinks that they can get continuous clinical benefit and if the sponsor agrees, those patients may continue taking DCC-2618 until presence of disease progression, death, or intolerable toxicity, or their demand to discontinue treatment. Such patients will only be monitored for all serious adverse events until 30 days after the last dose of investigational product or the initiation of new anti-tumor therapies (whichever is the first).

4 Study Population

4.1 Inclusion Criteria

The eligible subjects for this study must meet all of the following inclusion criteria:

1. Male or female patients ≥18 years of age.
2. Patients with histopathologically-confirmed advanced gastrointestinal stromal tumors.
3. Subjects who have progressed on previous treatments with imatinib, sunitinib and one or two other drugs or have documented intolerance to any of these treatments. Note: A documented intolerance must be after the dosage adjustment (including suspension and reduction).
4. ECOG PS of 0-2.
5. 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 investigational drug.
6. Patients of reproductive potential must agree to follow the contraception requirements.
7. Patient is capable of understanding and complying with the protocol. Signed written informed consent before any study-related procedures were performed.
8. Subject must have at least 1 measurable lesion (non-nodal lesions must be ≥ 1.0 cm in

the long axis or ≥ 2 times the slice thickness) according to the RECIST v1.1-GIST Specific Standard. A lesion with definite progression after local treatment can also be considered to be measurable. Radiographic examination results must be available within 21 days prior to the first dose of the investigational drug.

9. Good organ function and bone marrow reserve function, including:
   - Neutrophil count ≥ 1,000/μL
   - Hemoglobin ≥ 8 g/dL
   - Platelet count ≥75,000/μL
   - Total bilirubin ≤1.5*the upper limit of normal (ULN)
   - AST and ALT ≤3*ULN, and AST and ALT≤5*ULN in the presence of hepatic metastases
   - Serum creatinine ≤1.5*ULN or creatinine clearance ≥50 mL/min (based on Cockcroft-Gault estimation) Formulas for calculation:

   Note: within 2 weeks prior to the above laboratory assessments, patients should not receive granulocyte colony-stimulating factor, interleukin-11 or infusion of red blood cells or platelets or other blood products.

   - Prothrombin time (PT) or international normalized ratio (INR) or partial thromboplastin time ≤1.5 × ULN. Patients on a stable, maintenance regimen of anticoagulant therapy for at least 30 days prior to investigational drug administration may have PT/INR measurements >1.5 ×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 baseline) within 1 week prior to the first dose of investigational drug (excluding alopecia and ≤ Grade 3 clinically asymptomatic lipase, amylase, and creatine phosphokinase laboratory abnormalities).

4.2 Exclusion Criteria

Subject meeting any of the following criteria should not be enrolled in this study:

1. Treatment with anticancer therapy, including investigational therapy, or investigational procedures within 14 days or 5 x the half-life (whichever is longer) prior to the first dose of investigational drug. For prior biological therapies, eg, monoclonal antibodies with a half-life longer than 3 days, the interval must be at least 28 days prior to the first dose of investigational drug.
2. Prior treatment with DCC-2618.

3. Previously or currently has an additional malignancy that is progressing or required active treatment, which may interfere with the safety or efficacy evaluation of DCC-2618. If the patient is receiving the adjuvant therapy that is likely to be effective for GIST or should be excluded based on the protocol (see Section 5.9.3), the patient should not be included in this study.
4. Patient has known active central nervous system metastases.
5. New York Heart Association class II - IV heart disease, active ischemia or any other uncontrolled cardiac condition such as angina pectoris, clinically significant cardiac arrhythmia requiring therapy, uncontrolled hypertension or congestive heart failure.
6. Arterial thrombotic or embolic events such as cerebrovascular accident (including ischemic attacks) or hemoptysis within 6 months before the first dose of investigational drug.
7. Venous thrombotic events (eg, deep vein thrombosis) or pulmonary arterial events (eg, pulmonary embolism) within 3 months before the first dose of investigational drug. Patients with venous thrombotic events ≥3 months before the first dose of investigational drug on conventional anticoagulation therapy are eligible.
8. 12-lead electrocardiogram (ECG) demonstrating QT interval corrected by Fridericia's formula >450 ms in males or >470 ms in females at screening or history of long QT interval syndrome.
9. Left ventricular ejection fraction (LVEF) <50% at screening.
10. Use of strong or moderate inhibitors and/or inducers of cytochrome P450 (CYP) 3A4, including certain herbal medications (eg, St. John's Wort) and consumption of grapefruit or grapefruit juice within 14 days or 5 x the half-life (whichever is longer) prior to the first dose of investigational drug.
11. Use of known substrates or inhibitors of breast cancer resistance protein (BCRP) transporters within 14 days or 5 x the half-life (whichever is longer) prior to the first dose of investigational drug.
12. Major surgeries (eg, abdominal laparotomy) within 4 weeks of the first dose of investigational drug; Following major surgeries, >4 weeks prior to the first dose of investigational drug, all surgical wounds must be healed and free of infection or dehiscence.
13. 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.
14. Active viral infections such as human immunodeficiency virus, hepatitis B, hepatitis

C infection, etc.

15. Female patients who are pregnant or lactating or who are expected to become pregnant during the study treatment period
16. Known hypersensitivity to any component of the investigational drug. Patients with Stevenson Johnson syndrome in previous TKI treatment need to be excluded.
17. Gastrointestinal abnormalities including but not limited to:
    - inability to take oral medication
    - malabsorption syndrome
    - Requiring intravenous nutrition
18. Any active hemorrhages, excluding hemorrhoids or gum bleeding.

4.3 Procedure for handling of subjects who are enrolled incorrectly

Patients who do not meet the inclusion criteria should not be enrolled in the study, and no exceptions will be allowed to the specification. Subjects found to be ineligible for inclusion should not initiate the study treatment and must withdraw from the study. In the event of a subject who does not meet the inclusion criteria but is unintentionally given the investigational drug, the investigator should immediately notice the Sponsor. On the protocol-specified visit date, the subject should be asked to bring the investigational drug to the study site and not to take it until the pre-dose assessments are completed.

5 Study Treatment and Management

Therapeutic drug in the study is DCC-2618.

5.1 Description of investigational drug

Strength of DCC-2618 is 50 mg tablets taken orally. Formulation of active pharmaceutical ingredients (API) of tablet is 25% w/w amorphous dispersions and Hypromellose Acetate Succinate (grade H [HPMCAS-HG] multimer matrix [33.33%]). Other excipients include microcrystalline cellulose (Avicel PH-101) (29.84%), lactose 310 (29.83%), crosslinked polyvinylpyrrolidone (5%), fumed silica (CabOSil M5P) (1%) and magnesium stearate (1%).

5.2 Investigational Products

The investigational drug can be distributed only under the supervision of the investigator or authorized designated personnel and administered to subjects of the study only.

The investigator or designated personnel should instruct subjects to take the investigational drug according to the protocol;

- The investigational drug should be taken at the same time each day as far as possible.

- You can take it before or after a meal.
- The investigational drug should be taken as a whole, not squashed, chewed or dissolved in food or liquid.
- Subjects should record medication date, time and dose from 3 days before PK sampling to the date of PK sampling.
- On the visit date specified in the protocol, the subject should bring the drug to the study site, complete all pre-dose examinations, and evaluate as appropriate by the investigator before taking the drug on the same day. Administration date, time and dose should be recorded.

If the dose is increased to 150 mg BID, the investigator or designated personnel should instruct subjects to take the investigational drug according to the protocol.

- Subjects should take the investigational drug twice daily with an interval of at least 6 hours at the same time every day.
- Other requirements are same as administration at 150 mg QD.

If subjects forget to take the investigational drug at the predetermined time, subjects who receive 150 mg QD administration can take the missed dose within 8 hours and subjects who receive 150 mg BID administration can take the missed dose within 4 hours. The missed dose of the investigational drug should not be taken more than 8 hours or 4 hours after the predetermined time. The investigational drug can be taken at the predetermined time next day. On the protocol-specified visit date, subjects were instructed to bring their medication to the study site and not to take their study medication until the pre-dose assessments were completed.

If subjects vomit immediately after taking the investigational drug, the dose should not be supplemented and prophylactic antemetics can be used before the next dose.

5.2.1 Dose escalation

DCC-2618 will be continued after the subject has radiologically confirmed disease progression based on independent imaging review and the dose was escalated to 150 mg twice daily (BID) until the protocol-specified event of treatment discontinuation; For the assessment of efficacy in this part of patients, the diameter of the lesion before dose escalation (not at screening) should be used as the baseline diameter.

On the basis of independent radiology review, when subjects experience disease progression, they should be informed of other optional treatments.

5.3 Dose interruption and modification for investigational drug

Treatment interruptions or dose reductions or treatment termination will be permitted at any time during the study for subjects who experienced intolerable toxicity; study treatment may

be interrupted for subjects who experience toxicity, but no longer than 28 consecutive days of discontinuation. If subjects resume administration, the investigational should arrange subsequent visits according to the predetermined visit cycle and it is not influenced by drug discontinuation.

5.3.1 Dose discontinuation caused by medical procedures

If subjects need to undergo a surgery during the study, the degree of surgery and wound healing speed should be considered. It should be handled according to the following principles:

- Planned minimally invasive surgery: discontinue the investigational drug 3 days in advance, resume the investigational drug 3 days after the surgery.
- Planned major surgery: discontinue the investigational drug at least 5 days in advance; the investigator should discuss with the sponsor to determine when to resume the investigational drug after surgery.
- Unplanned major surgery: discontinue the investigational drug immediately; the investigator should discuss with the sponsor to determine when to resume the investigational drug after surgery.

5.3.2 Dose interruption and dose reduction due to adverse events

Treatment suspension and/or dosage reduction of the investigational drug or treatment termination will be allowed at any time during the study for subjects with an intolerant toxicity reaction of any levels. If the drug is resumed after dose suspension, calculation of visit cycle should be based on the predetermined arrangement and not influenced by dose suspension. See Table 6 for dose adjustment regimen.

If subjects can't tolerate 50 mg QD or experience disease progression based on independent radiology review after dose reduction, the study treatment should be terminated and subjects should enter the safety follow-up period and start survival follow-up.

All dose interruptions, reductions (including missed doses), downtitration, or uptitration, and reasons must be recorded on the eCRF form.

Table 6 DCC-2618 Dose Modification Scheme

	Initial dose	First reduction	Second reduction
Initial Patient	150mg QD	100mgQD	50mg QD
Patients whose dosage are increased to 150 mg BID after disease progression	150mg BID	100mgBID	150mg QD

If the adverse event resolves to grade 1 or baseline level and the drug is resumed, the subject will be allowed to resume the drug at the dose when the adverse event occurred. If the dose

for the subject has been reduced to the first reduced dose and the adverse event resolves to grade 1 or baseline level, the subject will be allowed to resume the drug at the initial dose. If the subject has experienced two consecutive reductions and the adverse event resolves to grade 1 or baseline level, the subject will be only allowed to resume the drug at the first reduced dose for at least one cycle (28 days) continuously and then use the drug at the initial dose.

If the adverse event does not resolve to grade 1 or baseline level within 28 days, the study treatment should be discontinued, unless the investigator evaluates that the adverse event is not clinically significant. After discussing with the sponsor, there may be an opportunity to resume the drug at a dose reduced by one level.

Table 7 Handling of dermatological toxicity and joint pain/myalgia and principles of dose adjustment

Severity of AE	Handling of AE and dose adjustment principles
Grade 1	Provide symptomatic and supportive treatment, and continue the drug at the original dose.
Grade 2	Provide symptomatic and supportive treatment, and continue the drug at the original dose. If the AE is not improved within 7 days, the treatment should be withheld: ● If the AE resolves to grade 1 or baseline level within 7 days, the drug can be resumed at the original dose; ● If the AE resolves to grade 1 or baseline level within 7 days, the drug can be resumed at a lower dose level; If the AE occurs for the second time, regardless of the time of resolving to grade 1 or baseline level, the drug can be resumed at a lower dose level. After reducing the dose, if AE remains grade 1 or baseline level for at least 2 consecutive cycles (56 days), the dose can be increased by one level.
Grade 3	Symptomatic and supportive treatment Withhold the invstigational drug for at least 7 days or until the AE resolves to grade 1 or baseline level (28 days at most). ● Resume medication at a lower dose level. After reducing the dose, if AE remains grade 1 or baseline level for at least 2 consecutive cycles (56 days), the dose can be increased by one level.
Grade 4	Discontinuation of study treatment. After the investigator evaluates and discusses with the sponsor, for non-life-threatening adverse events, medication can be continued.
Any Grade	Stevens-Johnson syndrome If patients have Stevens-Johnson syndrome (SJS), the investigational drug must be discontinued permanently. Patients should be sent to hospital immediately to receive clinical assessment and supportive treatment according to institutional guidance. Because there is risk of recurrence of SJS, the investigational drug should not be administered again.

Table 8 Handling of hypertension and principles of dose adjustment

Severity of AE	Handling of AE and dose adjustment principles*
Grade 1 (systolic BP 120-139 mmHg, diastolic BP 80-89 mmHg)	Start blood pressure monitoring; The original dose was continued.
Grade 2 (systolic blood pressure 140 - 159 mmHg, diastolic blood pressure 90 - 99 mmHg or elevation > 20 mmHg (diastolic blood pressure), with accompanying symptoms or elevation of previous normal blood pressure to 140 / 90 mmHg)	Adopt antihypertensive therapy to make diastolic blood pressure ≤ 90 mmHg or systolic blood pressure 140 ≤ mmHg. ● If previous blood pressure is in the normal range, monotherapy can be adopted; ● If the subject has previously adopted antihypertensive therapy, the dose should be increased; The original dose was continued. If the blood pressure elevates by > 20 mmHg (diastolic blood pressure) and there are accompanying symptoms, the treatment should be withheld until symptom resolution or diastolic blood pressure ≤ 90 mmHg; Medication can be resumed at the original dose.
Grade 3 (systolic blood pressure ≥ 160 mmHg, diastolic blood pressure ≥ 100 mmHg) or one additional drug required or more aggressive treatment required	Adopt antihypertensive therapy to make diastolic blood pressure ≤ 90 mmHg or systolic blood pressure 140 ≤ mmHg. ● Initiation of antihypertensive therapy and/or ● Increase the intensity of antihypertensive treatment and/or ● Add additional antihypertensive therapy If there are accompanying symptoms, the treatment should be withheld until diastolic blood pressure ≤ 90 mmHg and/or systolic blood pressure ≤ 140 mmHg and symptom resolution; Medication can be resumed at the original dose. If the blood pressure is inadequately controlled after adding one drug or enhancing antihypertensive therapy, the dose should be reduced by one level; If grade 3 hypertension occurs again, regardless of whether the dose has been reduced or antihypertensive therapy has been adopted, the dose should be reduced by one level again.
Grade IV (life threatening)	Handle according to treatment principles of local hospital; Discontinue the treatment with the investigational drug.

* If the blood pressure can be stably controlled within one cycle, the dose can be increased after investigator assessment.

Table 9 Treatment of AEs except for dermatological toxicity and joint pain/myalgia and hypertension and principles of dose adjustment

Severity of AE	Handling of AE and dose adjustment principles
Grade 2 weight loss or other grade 3 or 4 AEs	Withhold treatment until the AE resolves to grade 1 or baseline level; ● Reduce by one dose level; ● If the subject can tolerate the reduced dose level and the same AE does not occur for at least 3 consecutive cycles, the former dose level can be restarted;

Severity of AE	Handling of AE and dose adjustment principles
Asymptomatic grade 3 or 4 laboratory abnormality (including CPK and lipase) for ≤ 10 days	Monitor clinical symptoms closely and continue medication at the original dose; If related clinical symptoms are accompanied, treatment with the investigational drug should be withheld. If the investigator considers after evaluation that medication should be restarted for the patient's benefit, it is necessary to discuss with the sponsor to decide whether to restart medication.
Asymptomatic grade 3 or 4 laboratory abnormality (including CPK and lipase) for > 10 days	Monitor clinical symptoms closely; for grade 4 AEs, the treatment should be withheld until the AE resolves to grade 3; ● For asymptomatic CPK and lipase increased, the treatment does not need to be withheld; Once the AE resolves to grade 3, the drug can be resumed at the original dose or a lower dose level as per the decision of the investigator and the sponsor.
Clinically significant grade 3 or 4 laboratory abnormality (including CPK and lipase) for > 10 days	If related clinical symptoms are accompanied, treatment with the investigational drug should be withheld. If the investigator considers after evaluation that medication should be restarted for the patient's benefit, it is necessary to discuss with the sponsor to decide whether to restart medication.

5.4 Drug Packaging and Labeling

DCC-2618 provided by the sponsor is tablets, 50 mg/tablet, and will be packaged in high density polyethylene bottles sealed with child-resistant closures, 30 tablets/bottle.

Drug label will be prepared according to regulations.

5.5 Drug storage

DCC-2618 must be stored at 5 - 25 ℃ (41 - 77 ℉). Seal up, protected from light and moisture (such as places close to shower of the bathroom). The allowed storage temperature range is 2 - 27 ℃ (35.6 - 80.6℉).

Study sites should store the drugs at safe places with temperature monitoring and can obtain the drugs after obtaining authorization.

5.6 Medication compliance

In order to ensure subjects' compliance, the investigator or designated personnel should supervise all administrations at the site. At each visit, the investigator or designated personnel should review subject compliance and remind subjects of medication requirements.

If subject compliance is poor and not improved after education and training, the treatment should be discontinued.

5.7 Responsibilities for Reception, Storage, and Management of Investigational Drugs

It is the responsibility of the investigator to manage the investigational products and equipment on its study site that are provided by the sponsor. The investigational products and supplies must be recorded accurately in accordance with the protocol and national laws and regulations, supplied as required by the study at any time and maintained, stored, dispensed, used and disposed according to the regulations. The investigator should designate a person to receive, store, dispense and return all investigational drugs during the study, and to record the dispensing accurately. Drug dispensing management form should include subjects' identification number, quantity of the drugs and drug bottles dispensed and returned. The return of the drug from the subject to the study site should be marked as "returned" to separate from the drug not yet dispensed.

All dispensing and management records should be accessible to the Sponsor for review. Study monitors will verify according to drug dispensing management form and stored drugs. Designated drug managers will dispense the investigational drugs according to the study protocol and drug management manual and cooperate with monitors' audit.

5.8 Drug Recovery and Destruction

Subjects should be instructed to return all used and partially used drug bottles. The investigator or the designated personnel should correctly record all dispensed and returned investigational drugs, including date, quantity and patients who used the drug. Unused investigational drugs should be uniformly returned after the end of study to the sponsor for uniform destruction.

5.9 Prior and Concomitant Medications

5.9.1 Previous treatments

Previous treatments (including drug therapy and non-drug therapy and surgery) should be recorded from 30 days prior to signing the informed consent form and recorded in the original medical record and eCRF.

5.9.2 Prior Anti-Cancer Therapy

Any prior anti-tumor therapies should be recorded in the original medical record and eCRF.

5.9.3 Concomitant medication

All concomitant medications during the study, including vitamin supplementation, non-prescription medication and herbal medicines (generic name of drug, administration purpose, administration dose and time, etc.) must be recorded in the original medical record and the eCRF in detail from the date of the first dose to 30 days after the last dose.

5.9.3.1 Drugs Allowed to be Used

Subjects can use drugs for improving symptoms (e.g., analgesics, laxative and antiemetics).

Drugs (e.g., antacid) for increasing pH value of gastric juice are allowed to be used , as long as they are not used within 2 hours before and after taking the investigational drug.

5.9.3.2 Drugs to be avoided or used with caution

The following drugs should not be used or used with caution:

- Potent or moderate inhibitors or inducers of CYP2D6, CYP2C8 or CYP2E1. For related drugs, please refer to the website of the Indiana University, School of Medicinehttp://medicine.iupui.edu/clinpharm/ddis/main-table/
- Known substrates or inhibitors of P-glycoprotein 1 (permeability glycoprotein, also known as multidrug resistance protein 1 or MDR1). Refer to the website of FDA for related inhibitors: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table5-2 and https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table5-1 for MDR1.
- Known substrates of OATP1B1 and OATP1B3. Refer to FDA website for related drugs: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table5-1
- Drugs metabolized through CYP2C8, CYP2C9, CYP2C19 or CYP2D6. For related drugs, please refer to the website of the Indiana University, School of Medicine: http://medicine.iupui.edu/clinpharm/ddis/main- table/

For example:

  - Warfarin can be used under close monitoring since the investigational drug has an inhibitory effect on CYP2C9.
  - Clopidogrel should be avoided. The activity of clopidogrel should be dependent upon CYP2C19. The efficacy of clopidogrel may be reduced if combined with the investigational drug.

Considering that taking the investigational drug and the above drugs simultaneously may have potential drug interaction, any of the above drugs should be taken under close monitoring.

5.9.3.3 Prohibited Drugs

Some drugs and foods are prohibited from the start of the screening period to the end of

safety follow-up in this study. The following drugs should be prohibited:

- Potent or moderate inhibitors or inducers of CYP3A4, including some herbal medicines (e.g., St. John's wort), should be discontinued 14 days or 5 x half-life prior to the first dose of the investigational drug (whichever is longer). For related drugs, please refer to the website of the Indiana University, School of Medicine: http://medicine.iupui.edu/clinpharm/ddis/main-table/
- Grapefruit or grapefruit juice should be discontinued 14 days prior to the first dose of the investigational drug.
- Known substrates or inhibitors of BCRP transporter should be discontinued 14 days or 5 x half-life prior to the first dose of the investigational drug (whichever is longer). For related drugs, please refer to FDA website: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm
- Anti-tumor therapy, including investigational treatment, should be discontinued 14 days or 5 x half-life prior to the first dose of the investigational drug (whichever is longer). For prior biological therapies, eg, monoclonal antibodies with a half-life longer than 3 days, the interval must be at least 28 days prior to the first dose of investigational drug.

5.9.4 Accompanying treatment

All treatment operations must be recorded in the original medical record and the eCRF in detail from the date of the first dose to 30 days after the last dose.

Surgical resection or palliative radiotherapy during the study (including the intensive blood collection period) should not be conducted before communication with the Sponsor. If the investigator or the sponsor considers this meets subjects' best benefit, surgical resection or palliative radiotherapy can be performed. However, in PFS analysis, subjects should be deleted.

5.10 Other Notice to Applicants

To relieve potential risks of photostimulation/phototoxicity, patients should be instructed to avoid strong sunlight, fluorescent lamp and other ultraviolet radiation sources during the study. It is suggested all patients adopt protective skin care measures, including: sunscreen cream with a sun protection factor $\geq$ 30, hypoallergenic moisturizing cream or ointment suitable for dry skin, cleaning and caring the skin with soaps and detergents not containing perfume.

5.11 Channels to access the investigational drug after the end of the trial

The study endpoints and discontinuation criteria are based on disease progression by independent imaging review, so there is no plan to provide investigational drug or other study

intervention to patients after the end of the study or after any patient has withdrawn prematurely. The Sponsor will evaluate the possibility to continue providing DCC-2618 to study patients after the primary study endpoint and safety data collected in the study are evaluated.

6 Visit Schedule and Assessments

Visit schedule of the study is shown in Table 1. All times should be recorded in a 24-hour format (e.g., 23:20 other than 11:20 PM).

6.1 Screening

Before starting any study-related procedures, the informed consent form signed by the patients must be obtained.

The screening period was limited to 21 days.

For the screening test, if the patient is routinely examined during the diagnosis and treatment of GIST and completed within the corresponding time limit required by the protocol (such as 21-day screening window,7 days before the first dose of investigational drug, etc.), and the test requirements of the protocol are met, The results of these tests may be used as screening assessments if earlier than the informed consent is signed.

6.2 Re-screening

Subjects can receive re-screening after obtaining the approval of the sponsor. If patients have received re-screening, except for ophthalmological examination, other assessments in the screening period should be performed again. If radiographic examination and dermatologic examination are performed 21 days prior to the first dose of the investigational drug, the examinations are not need to be performed again. Patients can be re-screened once only. If patients enter re-screening, the screening window will be calculated after the start of the re-screening.

6.3 Study period

After confirming patients meet the inclusion criteria, the drug will be administered once on Day -7. Intensive blood collection will be carried out after that. Hospitalization is suggested during intensive blood collection. Continuous administration starts on C1D1 and subjects enter the study treatment period. See Table 1 for visits in the study period. All study visits should be carried out in the window.

All subjects who withdraw treatment should carry out visit at study site within 7 days after the last dose.

6.4 Follow-up

All subjects will receive safety follow-up 30 days (± 5 days) after the last dose and ask subjects through telephone adverse events after the last dose and drug therapies including

anti-tumor therapy and other treatments.

Survival follow-up should be carried out once monthly after that to ask subjects through telephone survival status and anti-tumor therapy condition.

6.5 Lost to Follow-up

If the following two conditions are met, it will be considered subjects are lost to follow-up:

- The subject has missed two consecutive visits and can't be contacted through telephone after the second missed visit (contacting through telephone for 3 times within 2 weeks).
- After the subject can't be contacted through telephone for 3 times, a registered mail is sent to the subject, but the subject does not reply within 2 weeks.

6.6 Study evaluation

This section will describe special assessments during the study in detail. See Table 1 for conventional assessments.

At any time during the study, if clinically indicated, unscheduled safety and efficacy assessment can be carried out.

6.6.1 Time points assessed

Examinations will be carried out according to time points described in Table 1.

6.7 Informed Consent Form

All patients should sign a written informed consent form before carrying out any procedures. The informed consent form approved by the sponsor, institutional review board (IRB)/independent ethics committee (IEC) should be used. The investigator should record informed consent process, including date of signing the informed consent form.

6.8 Assigned Subject No.

Each patients will be assigned a subject number after signing the informed consent form. If the patient receives re-screening, the original subject number will be used.

6.9 Demographics and Medical History

Demographic data must be collected during the screening period.

Tumor history and prior treatments (including reasons for treatment discontinuation):

- Known GIST histological diagnostic results.
- KIT/ PDGFRA gene mutation status.
- All prior anti-neoplastic therapies, including
- Surgery: including surgery date, site and method (e.g., only tumor tissue samples are

collected or R0, R1 and R2)

- Systemic therapy: including treatment date, drug (including dose and dosing regimen), treatment purpose (e.g., adjuvant therapy or treatment for metastases), best response, date of progressive disease or other reasons and date for treatment discontinuation.
- Radiation therapy: including site, total dose, date and treatment efficacy.
- Other treatments: such as radiofrequency ablation, including site, date and treatment efficacy.

Other medical history: any clinically significant diseases prior to signing the informed consent form should be collected during the screening period to evaluate whether patients have diseases listed in the inclusion and exclusion criteria. Medial history should include review of all organ and system, prior medical and surgical history and allergic history. Diseases that still exist when signing the informed consent form will be regarded as concomitant diseases and the starting date should be recorded.

6.10 Efficacy

6.10.1 Radiographic examination

All subjects will receive radiographic examination of the chest, abdomen and pelvis. See Table 1 for arrangement of time points.

Radiographic examination during the Screening Period should cover the chest, the abdomen and the pelvis (within 21 days before the first dose). Only abdomen and pelvis are examined during the study; for patients with pulmonary metastases in the screening period or pulmonary metastases symptoms during the study at the investigator's discretion, chest examination should be performed during the study. It is performed once in each of the first four cycles (including Cycle 4), and then once in every two cycles (e.g., Cycles 6, 8 and 10).

Radiographic examination must be performed within 21 days before the first dose of drug. Radiographic examination performed before signing an ICF can be used in the Screening Period as long as it is performed within 21 before the first dose and the examination method and result comply with the protocol. Radiographic examination can be performed within ±7 days of the scheduled visit . On the basis of independent radiology review, patients assessed as CR or PR in the first assessment should undergo confirmation at least 4 weeks later. Enhanced scan should be performed. If subjects are allergic to CT enhancer, MRI can be performed for abdominal and pelvic examinations and CT for chest examinations as long as examination methods are consistent during the study. Ultrasound examination cannot be performed.

If the subject discontinues treatment for reasons other than progressive disease, death, withdrawal of informed consent and lost to follow-up, the subject should receive radiographic

examination for tumor assessment by IRR after treatment withdrawal according to the frequency consistent with that during the study until presence of disease progression meeting "RECIST v1.1-GIST Specific Standard" or until starting of new anti-tumor therapy, whichever is the first.

Copies of all radiographic scans should be obtained and, according to the regulations, sent to the independent imaging supplier designated by the sponsor. The independent imaging supplier will assess imaging quality and be responsible for independent radiology review.

Independent imaging supplier must ensure independent radiology reviewers are blinded to investigator's assessment and other information. Before any independent radiology review, this procedure and all other radiographic images procedures will be recorded in the specified review rules of protocol between the sponsor and the independent imaging supplier.

Independent radiology reviewers and investigators will assess tumor response based on RECISTv1.1-GIST Specific Standard. Response confirmed by investigators will be recorded in the eCRF. Data from independent radiology review will be used for primary endpoint analysis.

Confirmation of absence of progressive disease: if independent radiology reviewers confirm there is no progressive disease, the patient will continue to receive treatment with the investigational drug, unless there are medical needs requiring discontinuation of the investigational drug (that is, rapid progression or clinical worsening). If investigators confirm progressive disease according to clinical worsening, scan should be performed and reviewed by independent radiology reviewers to confirm whether the patient has progression. Basis of confirming progressive disease as per clinical worsening should be recorded in patients' source documents and eCRF.

Confirmation of progressive disease: subjects who have radiologically confirmed progressive disease on the basis of independent radiology review can continue DCC-2618 treatment at a dose increased to 150 mg, BID; subjects who can benefit from DCC-2618 treatment but cannot tolerate the increased dose will continue DCC-2618 treatment, 150 mg QD; or discontinue DCC-2618 treatment. If subjects use the drug at the original dose, dose escalation will not be performed in the future.

6.10.2 Survival follow-up

All subjects should receive survival follow-up until withdrawal of consent inform, lost to follow-up or death for any reasons. After the safety follow-up, the investigator should call the subject to follow-up the survival status and anti-tumor therapy once monthly (±5 days).

6.11 Safety

Safety was assessed based on changes from baseline in physical examination, ECOG score, vital signs, ECG, left ventricular ejection fraction, dermatological examination and laboratory

parameters, and reported adverse events.

6.11.1 Physical examination

Comprehensive physical examination should be carried out in the screening period, including head/neck/thyroid gland, eye/ear/nose/throat, respiratory system, cardiovascular system, lymph node, abdomen, skin, muscle and musculoskeletal and nervous system. Breast, anorectum and reproductive organ examination will be carried out only if clinically indicated.

Targeted examinations can be carried out during the study (including the intensive blood collection period) according to clinical symptoms and subjects' chief complaints.

After the screening period, any clinically significant abnormal physical examinations must be recorded as AEs.

6.11.2 ECOG score

ECOG scoring will be carried out according to Table 1 before or after administration.

6.11.3 Vital sign and height

The time points of vital signs, including blood pressure, heart rate, respiration and body temperature, will be as specified in Table 1. Patients were to rest in a seated or recumbent position for at least 5 minutes before starting the examination.

Height is measured at the screening visit only.

6.11.4 Electrocardiogram

12-lead ECG examination will be performed according to Table 1-2 Schedule or at the time when any cardiac-related adverse event occurs during the study.

ECG examination should follow the following regulations:

- 12-lead ECG must be performed at least 15 minutes after the patient has a rest (in a supine or semi-recumbent position).
- ECG examination should be carried out before administration.

All ECG assessment items include:

- Heart rate
- PR interval
- QT interval: QTcB (Bazett's corrected QT interval [$QTcB = QT/(60/\text{heart rate})^{0.50}$] and QTcF($QTcF = QT\ (60/\text{heart rate})^{1/3}$)
- QRS wave group
- RR interval

6.11.5 Echocardiogram

All echocardiograms will be performed at time points outlined in Table 1 Schedule of Study Visits and may be used as a screening examination as long as the patient's echocardiogram is within 21 days prior to the first dose and is in compliance with protocol requirements. Left ventricular ejection fraction should be recorded in the original medical record and the eCRF.

6.11.6 Dermatologic examination

Dermatologic examination should be carried out according to the study visit schedule in Table 1 or if clinically indicated. The examinations must cover the whole skin. Special attentions should be paid to squamous cell carcinoma of skin, actinic keratosis and keratoacanthoma. If the dermatological examination is performed before signing an ICF, it can be used as one performed during the Screening Period provided that the examination is performed within 21 before the first dose and as per the protocol. Any new or changed skin damages from baseline during the study (including the intensive blood collection period) should be recorded in the original record and the eCRF. Once it is suspected as squamous cell carcinoma of skin or keratoacanthoma, biopsy skin should be carried out at study site and it should be diagnosed by qualified pathologist.

6.11.7 Ophthalmological examination

Ophthalmological examination should be carried out according to the study visit schedule in Table 1. If clinically indicated, consultation by qualified ophthalmologist should be carried out.

Examination includes anterior structures (including cornea, anterior chamber, iris and lens) and posterior structures (including optic nerve, yellow spot, retinal blood vessels, peripheral retina and vitreous body); intraocular pressure and vision should be evaluated.

Ophthalmological examination may not be repeated during the Screening Period, provided that it has been performed within 28 days before signing an ICF on the patient who discontinued previous anti-tumor therapy, with the examination report available, and that the examination conforms to the requirement of the protocol.

6.11.8 Laboratory test

All laboratory test time points will be performed according to the schedule of study visits in Table 1, and the test may be added according to the clinical judgment of the investigator.

All findings must be documented in the original medical record and recorded in the eCRF.

Abnormal laboratory test results, if considered to be clinically significant by the investigator, should be recorded as AEs.

Grade of laboratory test results should be judged in accordance with NCI-CTCAE V4.03.

The laboratory test items are shown in Table 10:

Table 10 Clinical laboratory tests

Serum biochemistry	Hematology and Coagulation	Urine routine
Glucose	Haemoglobin	
Blood urea nitrogen or urea	● Mean corpuscular hemoglobin	
Creatinine	● Mean corpuscular hemoglobin concentration	
Na	● Mean corpuscular hemoglobin volume	Protein
K	Hematokrit	Occult blood
Ca	PLT	Specific gravity
Mg	WBC	Ketone bodies
P	Reticulocyte	Glucose
Bilirubin total and Bilirubin direct	Differential and absolute white blood cell count:	
Alkaline phosphatase	● Neutrophils	
Aspartate aminotransferase	● Basophil (BASO)	
Alanine aminotransferase	● Eosinophils	
Lactic dehydrogenase	● Lymphocyte	
Creatine phosphokinase	● Monocytes	
Total protein	Blood coagulation function test	
Albumin	**Activated partial thromboplastin time**[1]	
Globulin	Prothrombin time	
Triglyceride	International normalized ratio	
Lipase		
Amylase		
Thyroid function test		
Thyrotropic hormone		
Tri-iodothyronine free		
Free thyroxine		

[1] For patients taking anticoagulants, coagulation tests will be performed according to Table 1. During the study, the blood coagulation function must be monitored according to appropriate clinical needs in case of any change in the dosage of anticoagulants.

6.11.9 Pregnancy tests

Serum pregnancy test needs to be performed on women of childbearing age within 7 days before the first dose, which is to be followed by a urine pregnancy test on Day 1 of each cycle as well as at the end of the study treatment, for confirmation of a negative result.

Female subjects without reproductive potential don't need to receive pregnancy test, defined as postmenopausal patients (amenorrhoea ≥ 12 months, follicle stimulating hormone ≥ 40 mIU/ mL) or patients with complete ovariectomy or amputation of uterus.

6.11.10 Contraception

Influence of DCC-2618 on sperm, conception, pregnancy and breastfeeding is unknown.

Subjects with reproductive potential should agree to adopt effective contraceptive methods. Male subjects and female subjects of childbearing potential should use adequate contraception during the study and for 6 months after discontinuation.

6.11.11 AE

All AEs should be evaluated, recorded and reported in accordance with ICH-GCP. Definition of AE, collection period, standard and procedure of recording, judgment and reporting of grade will be described in detail in Chapter 7.

6.11.12 Safety follow-up

All patients will receive safety follow-up to collect information of AEs and drug therapies including anti-tumor therapy and other treatment operations until 30 days (±5 days) after the last dose.

6.12 Pharmacokinetics

6.12.1 Blood sampling

In the study, intensive blood collection will be carried out in the first 10 - 15 enrolled subjects to measure blood concentration of DCC-2618 and its metabolite DP-5439.

Hospitalization is suggested for patients subject to intensive blood collection. Blood samples need to be collected on D-7 first, which is followed by administration with the drug once, and then intensive blood sample collection without taking the investigational drug until D-1. Collect blood sample once first for C1D1, which is to be followed by continuous administration with investigational drug from C1D1. The PK blood sampling schedule is presented in Table 11.

Table 11 Pharmacokinetic blood sampling time points

Study period	Time points of PK intensive blood collection (hour)														
	Pre-dose (-1h)	**0.5±2 min**	**1±3 min**	**2±5 min**	**4±10 min**	**6±10 min**	**8±20 min**	**12±20 min**	**24±1h**	**48±1h**	**72±1h**	**96±2h**	**120±2h**	**144±2h**	**168±2h**
D-7	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C1D15	X	X	X	X	X	X	X	X	X						
D1 (C2-C4)	X														

Except for subjects subject to intensive blood collection, other subjects don't need to receive intensive blood collection, but sparse blood collection should be carried out. The specific sampling time points are 6 hours ± 10 minutes after administration on C1D1, within 60 minutes before administration and 6 hours ±10 minutes after administration on C2D1; three PK samples will be collected from each subject at each sparse time point. Actual administration time and actual blood collection time should be accurately recorded.

Unscheduled blood samples may be requested by the Sponsor at the time of certain treatment-related AEs.

Bioanalysis laboratory will measure plasma sample concentration with LC-MS/MS.

If the dose was withheld due to adverse events in the first cycle and the subject is unable to receive steady-state intensive PK sampling at the predetermined visit, the investigator should discuss with study doctor of Zai Lab to determine whether the subject needs steady-state PK sampling in subsequent therapy. If necessary, steady-state PK sampling can be carried out at any time.

After PK sampling, the subjects can continue the treatment with DCC-2618, safety visits and efficacy evaluation, until the occurrence of an event for treatment termination as specified in the protocol.

Sample collection, labeling, processing, storage and transportation should be carried out in accordance with laboratory manual.

6.12.2 Blood samples and data analysis

After obtaining blood concentration of DCC-2618 and metabolite DP-5439 after single dose and multiple doses, the following PK parameters will be calculated with non-compartment model, including but not limited to C_{max}, T_{max}, AUC and $T_{1/2}$, etc. If necessary, group PK analysis of pharmacokinetic data will be carried out with industrial standard software on the basis of other clinical study data. Group PK report will be drafted independently and not regarded as the appendix of this study report.

7 Recording, grading and reporting of adverse events and serious adverse events

7.1 Definition of adverse events (AEs)

An adverse event is any untoward medical occurrence in a patient or subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. Example of AEs include, but not limited to adverse signs (including abnormal findings in laboratory test) and symptoms, conditions that have a temporal relationship with use of investigational drug, regardless of causal relationship to the investigational product. AEs include new events or previous diseases with deteriorated

severity or frequency after signing the informed consent form. Adverse events include serious adverse events (SAEs) and non-serious adverse events.

Planned hospitalization or surgery for underlying disease and potential disease progression before screening should not be reported as an AE, unless the disease deteriorates accidentally during the study (e.g., surgery performed in advance).

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as an AE. However, if diseases causing the implementation of these procedures meet regulations of AE in this protocol, they should be reported as an AE; in addition, if implementation of these procedures cause adverse influence to patients, they should be reported as an AE.

The severity must be judged immediately after the occurrence of an AE to confirm whether it is a SAE.

7.2 Judgment of severity

The investigator should confirm and record the severity of all AEs.

Severity of AEs should be evaluated from grade 1 to 5 on the basis of Common Terminology Criteria for Adverse Events (CTCAE).

For adverse events without designated CTCAE grade, criteria recommended by CTCAE may be referred to.

Grade I (mild)	Temporary symptom, treatment not indicated, subject's daily activities not influenced. Asymptomatic or mild symptoms; clinical or diagnostic observations only;
Grade II (moderate)	Mild discomfort in subject, daily activities slightly influenced, minimal, local or noninvasive intervention indicated;
Grade III (severe)	Intolerant symptoms, daily activities significantly influenced, drug therapy or other interventions indicated
Grade 4 (Life Threatening)	Life-threatening; urgent intervention indicated
5 (Death)	Results in death

7.3 Determination of drug relationship

The investigator should evaluate the causality between adverse event and the investigational drug according to the following table:

Related	Definitely related	Adverse event is related to administration of the investigational drug, there is rational possibility between the occurrence of the event and the investigational drug, and other reasons except for the investigational drug have been excluded; and/or the event reoccurs when the investigational drug is resumed
	Probably related	Adverse event is related to administration of the investigational drug, there is rational mechanism between the occurrence of the event and the investigational drug, and the event cannot be rationally explained by

		patients' clinical conditions, or there is not other obvious cause
	Possibly related	Adverse event is related to administration of the investigational drug and there is rational mechanism between the occurrence of the event and the investigational drug; however the event may be induced by other causes, such as patients' clinical conditions and features of underlying diseases.
Unrelated	Possibly unrelated	Adverse event is possibly not related to the investigational drug but possibly related to other factors. It is more rational to explain from other aspects (such as concomitant medications, concomitant diseases), or the causal relationship would be impossible in terms of temporal relation.
	Unrelated	The adverse event is related to other cause than the investigational drug (this cause should be recorded in the original medical record of the patient)

7.4 Measures Taken to the IMPs

The investigator must clarify measures to the investigational drug due to AE. Measures taken to the investigational drug are shown in the following table:

Category	**Definition**
Unchanged dosage	AE doesn't lead to dose adjustment
Dose reduction	AE leads to dose reduction
Treatment discontinuation	AE leads to dose interruption
Permanent discontinuation of drug	AE results in permanent discontinuation of drug
Not applicable	Select "not applicable" in case of any of the following conditions: ● AE occurs before the administration of the investigational drug; ● The subject died suddenly during treatment, so it is unable to take measures to investigational drug for this event; ● The investigational drug has been discontinued before the occurrence of the AE; ● The subject didn't take the drug when the AE occurs and the occurrence of the AE will not influence subsequent medication plan.

7.5 Outcome of adverse event

The investigator must follow all AEs until the final outcome. Outcome of AE can be recorded according to the following table:

Category	**Definition**
Recovered	AE recovered, without sequela
Recovered, with sequela	AE recovered, with sequela Select "not recovering/not resolving/persistent" for irreversible congenital anomaly. For other irreversible diseases, select "recovered, with sequela".
Recovering/resolving	AE resolving and recovering
Not recovering/not resolving/persistent	AE not recovering, persistent

Category	Definition
Death	Outcome of AE is death. Only when the death is possibly related to AE, can "Death" be used
Unknown	Outcome of AE is unknown, such as subject lost to follow-up

The investigator is required to continue to follow up any adverse event that has not recovered at the last visit of the study until the event is recovered or stable or resolved to baseline level or stable state of chronic diseases or it is unable to obtain more information (e.g., refusing to be followed up or lost to follow-up). Subsequent follow-up visits may not be entered into the eCRF, but the sponsor considers that there is a right to request further information from the investigator if necessary.

7.6 Treatment measures taken for AEs

The investigator should ensure appropriate medical care for any AEs. In addition, the investigator should record whether treatment measures have been taken for AE. If treatment measures have been given, such as other drugs, hospitalization, surgery or physiotherapy, "yes" should be recorded; if the above treatment is not given, "no" should be recorded.

7.7 Other considerations for AE

Evaluation of clinical significance

Laboratory test, ECG, physical examination and vital signs will be evaluated during the study and clinically significant abnormalities should be recorded as AEs. If possible, disease diagnosis should be first used as the name of adverse events (e.g., urinary tract infection and anemia). If the diagnosis is unable to be confirmed, abnormal test findings will be reported as AE (e.g., bacterial in urine or haemoglobin decreased). If the diagnosis is confirmed later, the diagnosis should be additionally recorded as an adverse event. If subjects meet one or several of the following conditions, abnormal study assessment will be regarded as clinically significant:

- Persistent deterioration from baseline, accompanied with corresponding symptoms or signs.
- Further diagnostic tests or drug/surgical therapies required.
- Leading to change in dose of the investigational drug, such as drug discontinuation or treatment termination.

The above criteria are not applicable to retesting to ensure whether test value is abnormal. Whether the study assessment is clinically significant should be judged by the investigator.

Grade 4 laboratory test indicator may be not a SAE, unless the patient's clinical status shows it is a life-threatening AE.

Symptoms of the studied disease should not be taken as AEs as long as these symptoms are progressive or expected progressive disease, including obvious deterioration, unless

deterioration is not caused by progressive disease and is part of the efficacy data the study will collect.

7.8 Defination of SAEs

An SAE is a serious adverse event that occurs during the course of a clinical trial and may include:

- Events leading to death;
- A life-threatening event (defined as an event in which the subject was at risk of death at the time of the event, not an event that hypothetically might have caused death if it were more severe);
- Events requiring hospitalization or prolongation of hospitalization;
- An event that results in permanent or significant disability/ incapacity/ impairment of work;
- Results in congenital abnormality or birth defect;
- Other important medical events, defined as an event that may not lead to death, be life-threatening, lead to hospitalization, but may jeopardize the subject or may require medical intervention to prevent one of above listed outcomes (e.g., allergic bronchospasm, aggressive treatment at emergency or home required, cachexia or convulsion, or drug dependence or drug abuse).

The following were not to be reported as SAEs:

- Any outcome, including death, due to progression of the patient's primary tumor disease as assessed by the investigator.
- Hospitalization or prolonged hospitalization due to economic issue or for purpose of reimbursement only.
- Elective surgery scheduled prior to the start of study treatment.
- Prescription or study-related examinations can be carried out only during hospitalization for hospital management reasons

7.9 Adverse Events of Special Interest (AESIs)

The following adverse events occurring after starting of the investigational drugs require special interest:

- Squamous cell carcinoma of skin
- Actinic keratosis
- Keratoacanthoma

Patients with squamous cell carcinoma of skin, actinic keratosis and/or keratoacanthoma

should be managed according to dermatologist and local guidance.

For the above adverse events of special interest, it is required to fill in the "AESIs Report Form" within 24 hours upon the investigator's awareness, and report to the sponsor via email: **saereporting@zailaboratory.com**. If the event meets the criteria for an SAE, it is required to fill in the “Clinical Study SAEs Report Form” and it will be reported directly to the sponsor according to the SAE reporting process.

7.10 Time Limit for Collection of Adverse Events

Collection and recording of adverse events (including SAE and AESI) will be carried out throughout the study, from the date of signing the informed consent form (ICF) to 30 days after the last dose of the investigational drug; if the patient starts new anti-tumor therapy, the deadline for collection of AEs will be the date of starting new anti-tumor therapy; any SAEs or AESIs occurring after the time limit for collection of AEs should be reported immediately if suspected to be possibly related to the investigational drug.

7.11 Requirements for reporting AE, SAE and AESI

Whether AE occurs should be monitored seriously in each subject. Information of AEs can be obtained by non-induced questions to subjects (e.g., how do you feel?) , signs and symptoms of clinical examination, observation of subjects and chief complaints of subjects. Information of AEs obtained by the above methods should be recorded in the original medical record and the eCRF.

If possible, disease diagnosis should be first used as the name of adverse events. If a unifying diagnosis is not available, then associated symptoms and signs are to be captured. Once the diagnosis is confirmed with the follow up information, the symptoms and sign should be replaced with diagnosis accordingly.

Any SAE occurring during the reporting period, whether or not related to the investigational drug, should follow the SAE reporting procedures of the relevant regulatory authorities or the Independent Ethics Committee.

The investigator should:

(1) If necessary, take appropriate medical measures immediately to ensure the safety of patients;

(2) Record SAEs in the AE Form, SAE Form and source documents of eCRF.

(3) The investigator should immediately fill in the “Clinical Study SAEs Report Form”, sign the name and date, and report it to the sponsor within 24 hours upon awareness of the event (public email mailbox of Drug Safety Department in Zai Lab: saereporting@zailaboratory.com).

(4) The course of the event was to be followed up and documented until recovery or

return to baseline values or until a clinically stable status was reached or the investigator agreed with the sponsor that no further follow-up was necessary. For the purpose of study analysis, events that are not recovered during the study report period should be recorded as persistent.

DCC-2618 may be continued until disease progression, death, or intolerable toxicity, or patient's request to discontinue treatment, in the opinion of the investigator, for patients who remain on investigational drug after the clinical trial database has been closed, if clinical benefit is sustained, Such patients will only be monitored for all serious adverse events until 30 days after the last dose of investigational product. The investigator should still collect information of drug management and accountability until all patients have finished the treatment.

- Treatment of Death Cases

All deaths occurring during the study, including within 30 days after the last dose of investigational drug, during the safety follow-up period of the last dose of investigational drug will be reported by the investigator as follows:

- If death is caused by disease progression, the investigator should notify the Sponsor's monitor of the event in the next site monitoring visit and record it in relevant section of eCRF, but it will not be reported as a SAE.
- If it is not determined whether the death is caused by disease progression, the AE should be reported as a SAE, informed to the monitor and reported to the relevant parties within 24 hours; the SAE report should evaluate whether the disease progression jointly contributed to the death of the subject and indicate the main cause of death and other related factors, as appropriate.
- Death cases with unknown causes must be reported within a specified time-line in accordance with the SAE, and the cause of death should be clarified with every effort. Autopsy may be conductive to assessment on the cause of death. If an autopsy is performed, the Sponsor should be notified of the autopsy report.

- Reporting and follow-up of AESI

AESI occurring in the reporting period should be reported to the sponsor within 24 hours of awareness. Follow-up on AESI will be pursued until they are recovered/resolved to the baseline level or clinically stable or the investigator and the sponsor consistently consider follow-up is not required. For the purpose of study analysis, events that are not recovered during the study report period should be recorded as persistent.

- Suspected unexpected serious adverse reaction (SUSAR)

If SUSAR related to the investigational drug occurs, the sponsor should expeditedly report to relevant regulatory authorities and all investigators and clinical trial institutions and ethics

committee taking part in the clinical trial. After receiving the relevant safety information of the clinical trial provided by the sponsor, the investigator should sign and read it in time, and consider whether to make corresponding adjustments to the treatment of the subject. If necessary, the investigator should communicate with the subject as soon as possible, and should report to the ethics committee SUSAR provided by the sponsor.

- Pregnancy

Effective contraception is required for both male and female subjects of childbearing potential during the trial and for 6 days after discontinuation of investigational drug. If a subject is found to be pregnant following initiation of study treat, the investigational drug will be permanently discontinued and the subject will be withdrawn from the trial. If a partner of a male subject becomes pregnant during the study or within 6 months after the last dose of investigational drug, the investigator should be informed immediately. The investigator must fill in the "Clinical Study Pregnancy Exposure Reporting Form" and expeditedly report to the sponsor via email upon 24 hours of becoming aware of pregnancy (**saereporting@zailaboratory.com**). At the same time, the pregnancy also must be recorded on eCRF. All pregnancies must be followed to conclusion to determine their outcome. If the outcome of the pregnancy meets SAE criteria (e.g., spontaneous abortion/miscarriage or therapeutic abortion with any detected congenital anomaly, stillbirth, neonatal death, or birth defect), it will be reported as SAE. The investigator should send the completed "SAE Reporting Form" to the Sponsor via email within 24 hours of becoming aware of the event. All pregnancies during the trial or within 180 days after discontinuation should be handled in accordance to the procedure described above. If necessary, the follow-up period will be prolonged to newborn.

7.12 Drug abuse, misuse, overdose and medical errors

Events related to drug abuse, misuse, overdose and medical errors should be reported to the sponsor.

AEs and SAEs related to drug abuse, misuse, overdose and medical errors should be recorded and reported according to corresponding requirements.

Note: Unintentional missing drug does not belong to medical error that must be reported.

8 Subject Withdrawal and Replacement

8.1 Subject withdrawal

Subjects can withdraw from the study or discontinue study treatment at any time. As long as clinical condition of subjects support, the investigator can discontinue subjects' treatment at any time. Reasons for subjects' treatment discontinuation or withdrawal from study may include the following types:

- Adverse Event

- Death
- Lost to Follow-up
- Poor compliance
- Investigator's decision
- Pregnancy
- After the first progressive disease based on independent radiology review, subjects who are unsuitable for dose escalation or continuing treatment at the original dose as per the investigator's assessment should discontinue the treatment.
- Progressive disease occurs again based on the investigator's assessment after increasing the dose to 150 mg BID.
- Protocol deviation
- Site Closure by Sponsor
- Termination of the study by the sponsor
- Subject's requests to withdraw
- The investigator considers the subject must discontinue the treatment for the subject's benefit.

If the subject discontinues treatment for reasons other than progressive disease, death, withdrawal of informed consent and lost to follow-up, the subject should receive radiographic examination for tumor assessment by independent radiologic review (IRR) after treatment withdrawal according to the frequency consistent with that during the study until presence of disease progression meeting "RECIST v1.1-GIST Specific Standard" or until starting of new anti-tumor therapy, whichever is the first.

If the subject voluntarily withdraws from the study, the investigator should contact the subject and ask the subject the reasons for treatment discontinuation and request the subject to return to study site to finish end of treatment visit (EOT) and safety follow-up and afterwards receive survival follow-up.

Subjects who discontinue treatment for other reasons must receive end of treatment (EOT) visit and safety follow-up and afterwards receive survival follow-up.

Patients should be asked to return all unused investigational drugs as far as possible.

In any case, the patient's final condition, particularly safety information, should be fully documented as far as possible.

8.2 Subject replacement

The study does not allow subject substitution.

9 Statistical Analysis

Please refer to Statistical Analysis Plan (SAP) for details of statistical analysis. Statistical Analysis Plan will be finalized before database locking. All changes in previously defined analytical procedures will be described in the final clinical study report (CSR).

Data cutoff of the study is 6 cycles after the last subject has been enrolled to the study or the time when at least 21 cases of IRR-based PFS have occurred in all enrolled patients, whichever occurs first, and the data will be locked for analysis.

9.1 Determination of sample size

This phase 2 bridging study is to prove the efficacy of DCC-2618 in Chinese patients is consistent with or similar to that in global patients using the primary endpoint of progression-free survival (PFS) on the basis of independent radiologic review.

Standard definition of bridging study success (consistent or similar): mPFS of ripretinib in Chinese patients will be statistically longer than 1 month, that is, the lower limit of bilateral 90% confidence interval of the observed mPFS is longer than 1 month. Statistical hypothesis: H_0: mPFS is 1 month; H_a: mPFS is 2.5 months; bilateral significant level is 0.1; assumed enrollment duration is 6 months; follow-up duration is 2 months; drop-out rate is 15% under at least a 90% test power; approximately 35 subjects should be enrolled to meet the test purposes.

9.2 Endpoints of study analysis

9.2.1 Primary endpoints

9.2.1.1 Efficacy

- Progression-free survival (PFS) based on independent radiologic review: assess PFS according to "RECIST v1.1-GIST Specific Standard" which include:
    - Lymph nodes cannot be taken as target lesions; enlarged lymph nodes will be followed as non-target lesions.
    - Bone lesions cannot be taken as target lesions;
    - Positron emission tomography (PET) cannot be used in efficacy assessment;
    - According to "RECIST v1.1-GIST Specific Standard", new tumor nodules within the pre-existing tumor lesion that are gradually growing must meet the following criteria before being determined as definite progression: (a) The lesion diameter should be at least 2 cm and confirmed as active GIST lesion (for example, using contrast or other criteria for enhanced scanning to rule out the possibility of false appearance); Or (b) At least 2 consecutive radiographic examinations indicative of enlarged lesion.

9.2.2 Secondary endpoints

9.2.2.1 Key secondary endpoints

9.2.2.1.1 Efficacy

- ORR based on independent radiology review: objective response rate, confirmed CR + confirmed PR.

9.2.2.2 Other secondary endpoints

9.2.2.2.1 Efficacy

- Overall survival (OS)
- TBR based on independent radiology review
- PFS based on investigator's assessment
- Disease control rate (DCR, CR+PR+SD) on Week 12 based on independent radiologic review

9.2.2.2.2 Safety

- Incidence and severity of treatment emergent adverse event (TEAE), adverse event of special interest (AESI) and serious adverse event (SAE) during the study (including intensive blood collection); severity will be assessed based on NCI-CTCAE V4.03.
- Incidence of adverse events resulting in dose adjustment, suspension and termination of the investigational drug;
- Changes from baseline in ECOG score, vital signs, ECG, left ventricular ejection fraction, dermatological examination and laboratory parameters.

9.2.2.2.3 Pharmacokinetics

- After obtaining blood concentration of DCC-2618 and metabolite DP-5439 after single dose and multiple doses, the following PK parameters will be calculated with non-compartment model, including but not limited to C_{max}, T_{max}, AUC and $T_{1/2}$, etc.

9.2.3 Exploratory endpoint

9.2.3.1 Efficacy

- PFS2 based on investigator's assessment: it is defined as the period from the first dose of investigational drug (150 mg, BID) to the first documented tumor progression or death from any cause (whichever is the first) after the dosage is increased to 150 mg (BID).

9.3 Analysis data sets

1) Intent-to-treat (ITT) - Subjects having signed the Informed Consent Form and been included in the trial.

2) Full analysis set (FAS): All patients who use at least one dose of the investigational drug.

3) Safety set (SS): All patients receiving at least one dose of the investigational drug. In the study, the definition of SS is consistent with FAS. SS is the main population for safety indicator analysis.

4) Efficacy analysis set (EAS): all subjects who enter the treatment period and have received at least one dose of the investigational drug, that is, all the patients who have started to receive continuous treatment with the investigational drug since C1D1.

5) PK analysis set: all subjects who received at least one dose of the investigational drug and have at least one blood concentration data of DCC-2618 or DP-5439 after administration.

6) Per protocol population (PP): subjects in FAS population who do not have expected protocol violations influencing efficacy and/or safety assessment (e.g., the enrolled patient does not comply with critical qualification criteria). Definition of per protocol population will be confirmed before database locking. The PP-based analysis will support the FAS-based analysis.

9.4 Statistical methods

9.4.1 General methods

Data collected in the study will be presented using summary tabulations and patients data tabulations. Continuous variables will be summarized with descriptive statistics (number of patients, mean, median, standard deviation, minimum and maximum). Categorical variables will be summarized with frequency and ratio. Time-event data will be summarized with the 25th, 50th (median) and 75th percentile and relevant bilateral 90% confidence interval using Kaplan-Meier (KM).

Unless otherwise specified, baseline measurement values should be the latest values prior to the first dose of the investigational drug. If not assessed, the last assessment before the visit will be used.

Medical Dictionary for Regulatory Activities (MedDRA) will be used to code medical history, adverse event and concurrent diseases. Prior and concomitant medications will be coded according to the Drug Dictionary of World Health Organization (WHODrug).

9.4.2 Subject disposition

All subjects who enter this study (that is, signing informed consent forms) will be summarized. In addition, number of subjects of each analysis data set and number of subjects deleted from each data analysis set (FAS, safety and PP, if applicable) will be summarized. Number and percentage of subjects who finish the study and number and percentage of

subjects who withdraw from the study and reasons for drug withdrawal will be summarized.

9.4.3 Demographic and baseline characteristics

Descriptive statistic methods will be used to summarize demographics, baseline features, medical history, and concomitant medications before dosing of the investigational drug and during the study in the FAS population.

9.4.4 Degree of exposure

Total subjects who receive treatment with the investigational drug will be summarized with number and percentage. Moreover, continuous descriptive statistics will be used to present number of cycles of treatment subjects receive. These analyses will be performed in efficacy analysis population.

9.4.5 Efficacy analysis

9.4.5.1 Primary endpoints:

PFS analysis based on independent radiology review

PFS based on independent radiologic review is defined as the time from the first dose of investigational drug (C1D1) to the first documentation of disease progression based on independent radiologic review or death due to any cause (whichever occurs first). Subjects who have previously received surgery for target lesion or non-target lesion, those who have previously received other anti-tumor treatments, and those whose progression or death date is not recorded for any reasons will be censored on the day of the last assessment.

EAS will be used as the main analysis set, with PP as the supporting analysis set. Sensitivity analysis of progression-free survival will be performed, which will be further described in SAP.

9.4.5.2 Key secondary endpoints

Critical secondary endpoint is ORR which is defined as the percentage of patients whose efficacy is confirmed as CR or PR based on independent radiologic review after the first dose of the investigational drug (C1D1). This analysis will be carried out in the EAS population as the main analysis and in the PP population as supportive analysis. Confirmation of CR or PR should be carried out at least 4 weeks after patients are first assessed as CR or PR.

9.4.5.3 Other secondary endpoints

9.4.5.3.1 OS

OS is defined as the time from the first dose of investigational drug (C1D1) to all-cause death. Surviving patients or those lost to follow-up will be censored on the day of the last assessment. This analysis will be carried out in the EAS population.

9.4.5.3.2 TBR based on independent radiology review

TBR based on independent radiologic review is defined as the time from the first dose of the investigational drug (C1D1) to the confirmed best response (CR or PR) (calculated based on the unit of week),

TBR analysis will be carried out in the population reaching response with descriptive statistical methods.

9.4.5.3.3 PFS assessment by investigators

PFS assessed by investigators is defined as the duration from the first dose of investigational drug (C1D1) to the first documentation of disease progression by the investigator or all-cause death (whichever occurs first).

9.4.5.3.4 DCR

Disease control rate at week 12 will be calculated and summarized with number and percentage. Disease control will be defined as complete response or partial responses or stable disease. This analysis will be carried out according to time point.

9.4.5.4 Exploratory endpoint

PFS2 based on investigator's assessment: it is defined as the period from the first dose of investigational drug (150 mg, BID) to the first documented tumor progression or death from any cause (whichever is the first) after the dosage is increased to 150 mg (BID). Subjects who have previously received surgery for target lesion or non-target lesion, those who have previously received other anti-tumor treatments, and those whose progression or death date is not recorded for any reasons will be censored on the day of the last assessment. For patients who are not assessed after dose increase, the date of the first dose of the investigational drug (150 mg, BID) will be taken as the censoring date.

9.4.6 Safety analysis

9.4.6.1 AE

The number and percentage of patients in the safety population experiencing AEs will be summarized with system organ class and preferred term.

Only TEAEs will be included in tabulations and TEAE is defined as any AEs newly occurring after the date of the first dose of the investigational drug until 30 days after the last dose of the investigational drug or those with a higher CTCAE grade.

Toxicity grade of adverse events will be classified with NCI-CTCAE V4.03. If a patient has the same SOC or preferred term for several times, only the severest event will be summarized as this SOC and preferred term in tabulation. Adverse events ≥ grade 3 will be summarized. Assessment and calculation will not be performed if there is no grade of toxicity.

SAEs and the AEs and AESIs that lead to dose suspension, reduction or discontinuation will be analyzed.

9.4.6.2 ECOG score, vital signs, echocardiogram and laboratory indicators

Overall summary of ECOG score, vital signs, echocardiogram and laboratory indicators will be performed with continuous descriptive statistical method according to time point. In addition, changes in continuous variables from baseline will be summarized. Categorical variables will be summarized with number and percentage.

9.4.6.3 Dermatologic assessment

Dermatologic assessment will be summarized with number and percentage.

9.4.7 Pharmacokinetics analysis

Descriptive statistics of PK parameters will be carried out.

10 Quality Control and Assurance

10.1 Monitoring

The Sponsor will designate a CRA for on-site monitoring. The CRAs should operate in compliance with the company's standard operation procedure (SOP). They should perform regular visits from the start to the end of study.

The CRA will have access to relevant original data of the clinical study, and review eCRF according to SOP to confirm information completeness, accuracy and consistency with original data.

Source data, eCRFs, copies of laboratory data, and medical test results must be readily available to the clinical monitor, IRB/ IEC, and regulatory authorities. The monitor should review all eCRF and informed consent forms.

10.2 Source Data Verification

The investigator must appropriately handle all data obtained during the clinical study to ensure rights and privacy of patients participating in the clinical study. The investigator must permit the monitor/auditor/inspector to consult and review required clinical study data to verify accuracy of original data and learn about study progress. If the original records cannot be verified, the investigator should agree to assist to further validation of data with them.

10.3 Audit

The quality of all drugs and materials used in the clinical study must be controlled. The sponsor, personnel authorized by the sponsor or related medical management institutions have the right to audit the clinical study in order to ensure the authenticity of the clinical study data and abide by the provisions of the clinical study protocol. Patients participating in the clinical study will be informed of the audit, but the privacy and data of patients will be

strictly protected.

10.4 Protocol compliance

The investigator should conduct the study in compliance with the study protocol and obtain the approval of IRB/IEC and corresponding regulatory authorities.

The protocol should not be changed without the approval of the sponsor. The changes should involve the sponsor and the investigator. Any amendment to the protocol must be recorded in detail, and the amendment should be signed, signed and dated by the investigator and the sponsor at least. The amendment should be submitted to the Ethics Committee for review and approval before implementation of the amendment. The sponsor should ensure all changes be submitted to regulatory authorities according to management regulations.

In case of other accidents needing to deviating from the protocol, monitor should consult with relevant personnel of the sponsor (and IRB, IEC, if necessary) to confirm an appropriate action plan.

The investigator should record information of all protocol deviations in the original data. For major protocol deviations, the investigator should notify the sponsor, IRB and IEC. Major protocol deviations include but are not limited to behaviors involving fraud or misconduct, increasing risks to patients' health or interpretations confusing study assessment.

11 DATA MANAGEMENT AND DATA RETENTION

11.1 Electronic Case Report Form (eCRF)

The sponsor will provide the eCRF and training for study sites.

The CRO working on behalf of Zailab is responsible for data management, so as to ensure the authenticity, integrity, privacy and traceability of the clinical study data. Data management by CRO authorized by the sponsor.

Data of each patients should be entered into the eCRF. The investigator should be responsible for the accuracy, authenticity as well as timely collection and reporting of all clinical, safety and laboratory data entered into the eCRF and any other data collection forms.

The investigator or personnel authorized by the investigator should enter the information into the eCRF as soon as possible after collecting the information. Medium

Upon completion of the original data entry by the investigator or authorized personnel, any changes made to the eCRF will be automatically recorded in the system and the audit trail will show the user's identification information and the date and time of any corrections. The eCRF should be signed by qualified study personnel in an electronic form to prove data in the eCRF (including any changes in the eCRF) are correct.

A complete eCRF is exclusive property of the sponsor and should not be supplied to third parties in any forms without written permission of the sponsor, except for the authorized

personnel of the sponsor or relevant regulatory authority.

11.2 DATA RETENTION

To make regulatory authorities or the sponsor can carry out assessment and/or review, study personnel agrees to retain the identity (including adequate information of records, e.g., eCRF and hospital record) of all participating patients, all original signed informed consent forms, eCRF, SAE forms, tracing documents, detailed records of treatment management and relevant correspondence (e.g., letters, minutes and telephone report). The investigator should retain records according to ICH, local regulations or regulations in clinical study protocol, whichever is longer.

If study site can't continue keeping study records in the required period for any reasons (e,g, movement), the sponsor should be notified in advanced. Study records should be transferred to the acceptable personnel designated by the sponsor, e.g., other institutions. The investigator should obtain written permission of the sponsor before dealing with any records, even if the retention requirements have been met.

12 Ethics

12.1 Ethics

This clinical study shall be implemented and reported in accordance with the Declaration of Helsinki, Chinese Good Clinical Practice and regulations.

The investigator should ensure the study is completely in compliance with regulations on protecting human subjects specified in 21 CFR Part 50, 21 CFR Part 54, 21 CFR Part 56, 21CFR Part 312, 21 CFR Part 314 and ICH GCP E6.

Before initiating a trial, the investigator should obtain approval from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, informed consent form and any other written information to be provided to subjects.

Before initiation of the clinical trial, approval must be obtained from the Ethics Committee. The approval issued by the Ethics Committee shall be made available to the investigator in written form. The investigator is obligated to provide the sponsor of a copy of the approval. The Ethics Committee approval should clearly list all the committee members involved in the review with their respective responsibilities.

During the clinical study, any of issues related to the patient safety of the clinical study, such as changes in the clinical study protocol or patient informed consent form as well as serious adverse events in the clinical study, must be reported to the Ethics Committee in a timely manner. The completion or premature termination of the clinical study must also be reported to the Ethics Committee.

12.2 Informed Consent Form

All parties should ensure to protect patients' personal data and not disclose patients' name in any forms, reports, publications or any other public data, unless otherwise required by laws. The sponsor should keep high-standard confidentiality and protection of patients' individual data during data transmission.

Informed consent form should be in compliance with ICH GCP, requirements of regulations and laws.

Informed consent forms used in this study and any changes during the study should be approved before use by the IRB/IEC and the sponsor.

The investigator has the responsibility to explain to each patient the purpose, methods, benefits and potential risks of this clinical study. Signed informed consent must be obtained before conducting any study-specific procedures. Informed consent should be expressed in written form. The informed consent must be dated and signed by the patient him/herself. For those patients who could not sign the informed consent form by themselves for any reasons, their parents, legal guardians, or protectors should sign the informed consent form. The original signed informed consent form and the process of obtaining informed consent should be preserved and documented in the electronic case report form and relevant trial source documents by the investigator.

By signing the informed consent form, the patient must also agree to allow the sponsor, the drug approval authorities, and the auditor and (or) the monitor to check and verify the obtained source data and materials related to clinical study, and all parties mentioned above must comply with confidentiality statement.

12.3 IRB/IEC

The investigator has the responsibility to ensure IRB/IEC approves the study protocol, protocol amendment, informed consent form and other related documents (e.g., recruitment advertisement, if applicable) in advance. All correspondences with IRB/IEC should be kept in study site's file.

Amendment can be initiated before obtaining the approval of IRB/IEC only when changes should be made to eliminate obvious direct harm to patients. In such case, the investigator should notify the IRB/IEC and the sponsor in wirtten immediately after implementation.

12.4 Patient Privacy

The Investigator must ensure that the confidentiality of the information about the Sponsor and the investigational drug provided or disclosed by the Sponsor for the clinical study, and such information can only be used upon authorization by the Sponsor.

The commitment is independent, effective and sustained until the permission of the Sponsor.

The Investigator also commits to keep confidentiality to a third party for any confidential information provided or disclosed by the Sponsor and the investigational products. Any intention to use such information must be approved by the Sponsor and agreed upon.

Investigators are obligated to protect the privacy of patients participating in clinical study. In all the documents submitted to the sponsor, the identity of any patient in the clinical study will be coded by the clinical trial identification number, while the patient's name, admission number should not show up. The investigator must appropriately keep name and address of clinical trial patients, as well as enrollment table corresponding to clinical study patient number. These enrollment tables will be strictly kept confidential and stored by the investigator.

The sponsor and personnel designated by the sponsor confirm and maintain the principles of patients' privacy right. Source data of patients can be linked to the sponsor's clinical study database or document only through the unique identification number throughout the study. If permitted by all applicable laws and regulations, limited patient properties (e.g., gender, age or date of birth) can be used to validate patients and the accuracy of unique identification number of patients.

To comply with ICH GCP and validate whether the protocol is followed, the sponsor will ask the investigator to allow its monitor or designated personnel, representative of any regulatory authority (e.g., FDA), auditor designated by the sponsor and corresponding IRB and IEC to review patients' original medical record (source data or document), including but not limited to any genetic/genome data, laboratory test reports, ECG reports, admission and discharge summary before patients are enrolled to the study, hospitalization and autopsy report during patients' participation in the study. Access to original medical record of patients needs special authorization of patients as part of informed consent process.

Some personal identity information (that is, name of patient, address and other information not collected in the patient's eCRF) should be deleted from copies of any patient-sourced documents supplied to the sponsor.

13 Termination of study

If the sponsor has learned about information of quality, efficacy and safety of the investigational drug and other important information that may influence correct conduct of the clinical study, the sponsor may discontinue the clinical study and send a written notice to the investigator and notify study discontinuation and reasons for discontinuation.

If the investigator plans to discontinue participation in the study, the sponsor must be informed immediately and the reason for discontinuation must be informed.

13.1 Criteria for Suspension or Early Termination of the Study

Criteria for suspension or early termination of the study include:

1. New information of safety or efficacy of the investigational drug is obtained and indicates changes in known risks/benefits of the compound, making patients participating in the study do not have acceptable risks/benefits any more.
2. Seriously violate GCP and influence the realization of the primary objective or threaten patients' safety.
3. The sponsor can suspend or prematurely terminate the study for reasons unrelated to the study.

13.2 Criteria for Premature Termination or Suspension of Study Sites

If it is found that the study site (including the investigator) seriously violates GCP, the protocol, contract/agreement or is unable to ensure normal conduct of the study, the study site may prematurely terminate or suspend the study.

13.3 Procedures for Early Termination or Suspension of the Study or Study Site

If the sponsor chooses to terminate or suspend the study or participation of study site, the sponsor will provide specific procedure for premature termination or suspension. Study sites for which the procedure is applicable should abide by the procedure.

14 Paper publication

Zai Lab (Shanghai) Co., Ltd., as the sponsor, has exclusive rights to this study. The manuscript and publication will reflect the cooperation among investigators and investigator's institution and Zai Lab. Authors will be identified before drafting of the manuscript. Many study institutions and investigators are participating in this study, unless prior consent has been obtained from Zai Lab, individual participating institution or investigator shall not publish any data related to the clinical study. Zai Lab has the final right to determine how the manuscript and its relevant publication will be disclosed.

15 References

1. Demetri GD, Jeffers M, Reichardt P, Kang Y-K, Blay J-Y, Rutkowski P, et al. Mutational analysis of plasma DNA from patients (pts) in the phase III GRID study of regorafenib (REG) versus placebo (PL) in tyrosine kinase inhibitor (TKI) refractory GIST: Correlating genotype with clinical outcomes. J Clin Oncol 31, 2013 (suppl; abstr 10503).
2. Ashman LK, Griffith R. Therapeutic targeting of c-KIT in cancer. Expert Opin Investig Drugs 2013;22(1):103-15.
3. Beadling C, Jacobson-Dunlop E, Hodi FS, Le C, Warrick A, Patterson J, et al. Kit gene mutations and copy number in melanoma subtypes. Clin Cancer Res 2008;14(21):6821-8.
4. Kemmer K, Corless CL, Fletcher JA, McGreevey L, Haley A, Griffith D, et al. KIT Mutations are common in testicular seminomas. Am J Pathol. 2004;164(1): 305-13.
5. Malaise M, Steinbach D, Corbacioglu S. Clinical implications of c-Kit mutations in acute myelogenous leukemia. Curr Hematol Malig Rep 2009;(2):77-82.
6. Verstovsek S. Advanced systemic mastocytosis: the impact of KIT mutations in diagnosis, treatment, and progression. Eur J of Haematol 2013;(2):89-98.
7. Care RS, Valk PJ, Goodeve AC, Abu-Duhier FM, Geertsma-Kleinekoort WM, Wilson GA, et al. Incidence and prognosis of c-KIT and FLT3 mutations in core binding factor (CBF) acute myeloid leukaemias. Br J Haematol 2003;121(5):775-7.
8. Koch CA, Gimm O, Vortmeyer AO, Al-Ali HK, Lamesch P, Ott R. Does the expression of c-kit (CD117) in neuroendocrine tumors represent a target for therapy? Ann NY Acad Sci 2006;1073:517-26.
9. Saini M, Jha AN, Abrari A, Ali S. A subset of human gliomas shows over-expression of KIT without its amplification. Gene 2012;497(2):155-63.
10. Went PT, Dirnhofer S, Bundi M, Mirlacher M, Schraml P, Mangialaio S, et al. Prevalence of KIT expression in human tumors. J Clin Oncol 2004;22(22):4514-22.
11. Heinrich MC, Corless CL, Blanke CD, Demetri GD, Joensuu H, Roberts PJ, et al. Molecular correlates of imatinib resistance in gastrointestinal stromal tumors. J Clin Oncol 2006;24(29):4764-74.
12. Liegl B, Kepten I, Le C, Zhu M, Demetri GD, Heinrich MC, et al. Heterogeneity of kinase inhibitor resistance mechanisms in GIST. J Clin Pathol 2008;216(1):64-74.
13. Gajiwala KS, Wu JC, Christensen J, Deshmukh GD, Diehl W, DiNitto JP, et al. KIT kinase mutants show unique mechanisms of drug resistance to imatinib and sunitinib in gastrointestinal stromal tumor patients. Proc Natl Acad Sci USA. 2009;106(5):1542-7.

14. Garcia-Montero AC, Jara-Acevedo M, Teodosio C, Sanchez ML, Nunez R, Prados A, et al. KIT mutation in mast cells and other bone marrow hematopoietic cell lineages in systemic mast cell disorders: a prospective study of the Spanish Network on Mastocytosis (REMA) in a series of 113 patients. Blood. 2006;108(7):2366-72.

15. Maleddu A, Pantaleo MA, Nannini M, Biasco G. The role of mutational analysis of KIT and PDGFRA in gastrointestinal stromal tumors in a clinical setting. Journal of Translational Medicine. 2011;9:75.

16. Dagher R, Cohen M, Williams G, Rothmann M, Gobburu J, Robbie G, et al. Approval summary: imatinib mesylate in the treatment of metastatic and/or unresectable malignant gastrointestinal stromal tumors. Clin Cancer Res 2002;8(10):3034-8.

17. Blanke CD, Rankin C, Demetri GD, Ryan CW, von Mehren M, Benjamin RS, et al. Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase. J Clin Oncol 2008;26(4):626-32.

18. Kee D, Zalcberg JR. Current and emerging strategies for the management of imatinib-refractory advanced gastrointestinal stromal tumors. Ther Adv Med Oncol 2012;4(5):255- 70.

19. Demetri GD, Benjamin RS, Blanke CD, Blay JY, Casali P, Choi H, et al; NCCN Task Force. NCCN Task Force Report: Optimal management of patients with gastrointestinal stromal tumor (GIST) – update of the NCCN clinical practice guidelines. J Natl Compr Canc Netw 2007;5(2):S1-29.

20. Aubin F and Blanke CD. Metastatic gastrointestinal stromal tumors. Cancer Chemother Pharmacol. 2011;67(Suppl 1):S9-S14.

21. Wang Zhenhua, et al. Epidemiological investigation on gastrointestinal stromal tumor in Shanxi province in 2011. National Medical Journal of China, 2013.93 (32): p.2541-4.

22. Minzhi Lv, et al. Incidence and Survival Analysis of Gastrointestinal Stromal Tumors in Shanghai: A Population-Based Study from 2001 to 2010. Gastroenterology Research and Practice. Volume 2014, Article ID 834136.

23. Blay J-Y. A decade of tyrosine kinase inhibitor therapy: Historical and current perspectives on targeted therapy for GIST. 2010. Cancer Treat Rev. 2011 Aug;37(5):373- 84.

24. Corless CL, Fletcher JA, and Heinrich MC. Biology of gastrointestinal stromal tumors. J Clin Oncol. 2004;22(18):3813-25.

25. Corless CL, Barnett CM, and Heinrich MC. Gastrointestinal stromal tumours: origin and molecular oncology. Nature Reviews. Cancer. 2011;11:865-78.

26. Emile JF, Brahimi S, Coindre JM, et.al. Frequencies of KIT and PDGFRA mutations in the MolecGIST prospective population-based study differ from those of advanced GISTs. Med Oncol. 2012 Sep;29(3):1765-72.

27. Eisenberg BL and Smith KD. Adjuvant and neoadjuvant therapy for primary GIST. Cancer Chemother Pharmacol. 2011;67 (Suppl 1):S3–S8.

28. Kang YK, Ryu MH, Yoo C, Ryoo BY, Kim HJ, Lee JJ, et al. Resumption of Imatinib dosing to control metastatic Gastrointestinal Stromal Tumors (GIST) after failure of Imatinib and Sunitinib: Results of a randomised, placebo-controlled, phase 3 trial (RIGHT). Lancet Oncol. 2013 November;14(12):1175–82.

29. Yoo C, Ryu MH, Nam BH, Ryoo BY, Demetri GD, Kang YK. Impact of imatinib rechallenge on health-related quality of life in patients with TKI-refractory gastrointestinal stromal tumours: Sub-analysis of the placebo-controlled, randomised phase III trial (RIGHT). Eur J Cancer. 2016 Jan;52:201-8.

16 Annexes

Annex 1 Response Evaluation Criteria in Solid Tumors - GIST Specific Standard (RECISTv1.1-GIST Specific Standard)

"RECIST v1.1-GIST Specific Standard" include:

- Lymph nodes cannot be taken as target lesions; enlarged lymph nodes will be followed as non-target lesions.
- Bone lesions cannot be taken as target lesions;
- Positron emission tomography (PET) cannot be used in efficacy assessment;
- According to "RECIST v1.1-GIST Specific Standard", new tumor nodules within the pre-existing tumor lesion that are gradually growing must meet the following criteria before being determined as definite progression: (a) The lesion diameter should be at least 2 cm and confirmed as active GIST lesion (for example, using contrast or other criteria for enhanced scanning to rule out the possibility of false appearance); Or (b) At least 2 consecutive radiographic examinations indicative of enlarged lesion.

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

Annex 2 Eastern Cooperative Oncology Group (ECOG) Performance Status Score

Description of physical status	Score
Completely normal, being able to perform work before illness without restriction	0
Not able to carry out heavy physical work, but be able to walk around and carry out light physical work such as light housework or office work	1
Can move around, capable of self-care, but unable to carry out any work-related activities, confined to bed for less than 50% of the day	2
Self-care can only be achieved to a limited extent, with more than 50% of the daytime spent in bed rest or chair sitting	3
Complete loss of activity of daily living, unable to achieve selfcare, confined to bed or wheelchair	4
Death	5