Clinical Study Protocol

Study Title:	A phase 2, randomized, multicenter, open-label study of DCC-2618 (ripretinib, ZL-2307) vs sunitinib in patients with advanced gastrointestinal stromal tumors after treatment with imatinib
Project No.:	ZL-2307-003
Version No. and Version Date:	February 25, 2021/Version 2.0
Study Drug:	DCC-2618 (Ripretinib, ZL-2307)
Study phase:	Phase 2 Study
Sponsor:	Zai Lab (Shanghai) Co., Ltd.
Principal Investigator:	[redacted]

Statement of Confidentiality

Signature page (Sponsor)

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Clinical Study Number: ZL-2307-003

The clinical study protocol has been approved by the sponsor.

Signature: _____ **Date:** _____

Protocol Synopsis

Name of Sponsor/Company	Zai Lab (Shanghai) Co., Ltd.
Study Title	A phase 2, randomized, multicenter, open-label study of DCC-2618 (ripretinib, ZL-2307) vs sunitinib in patients with advanced gastrointestinal stromal tumors after treatment with imatinib
Protocol Number	ZL-2307-003
Study Phase	Phase 2
Study Site	Beijing Cancer Hospital etc
Investigator	[redacted]
Number of Subjects Planning to be Enrolled:	About 98
Study Objectives	Primary objective: • To assess the efficacy (progression-free survival [PFS], by independent radiologic review) of DCC-2618 (ripretinib, ZL-2307) and sunitinib in patients with advanced gastrointestinal stromal tumors after treatment with imatinib Secondary objective: • To assess objective response rate (ORR) by independent radiologic review using RECIST v1.1-GIST-specific criteria • To assess disease control rate (DCR) by independent radiologic review • To assess PFS based on Investigator assessment • To assess overall survival (OS) • To compare the safety profile of DCC-2618 (ripretinib, ZL-2307) to the safety profile of sunitinib • To assess pharmacokinetic characteristics of DCC-2618 (ripretinib, ZL-2307) Exploratory objective: • To evaluate potential biomarkers in blood or tumor tissue which might predict response to DCC-2618 (ripretinib, ZL-2307) ○ To understand potential drug resistance mechanism to DCC-2618 (ripretinib, ZL-2307) in GIST. ○ To characterize KIT and PDGFRA mutations at baseline and DCC-2618 (ripretinib, ZL-2307)-driven longitudinal mutant allele frequency changes in plasma. Note: Blood samples and tumor tissues for exploratory purpose will be collected after obtaining the approval of China Human Genetic Resources Administration Office.
Study Design	This is a randomized, open-label, multicenter phase 2 clinical study to compare the efficacy and safety of DCC-2618 (ripretinib, ZL-2307) to sunitinib in GIST patients who progressed on or were intolerant to first-line anticancer treatment with imatinib.

	Approximately 98 patients will be randomized in a 1:1 ratio to DCC-2618 (ripretinib, ZL-2307) 150 mg QD by continuous administration or sunitinib 50 mg QD, 4 weeks on, 2 weeks off. Up to 10% of randomized patients may have KIT/PDGFRA WT GIST (wild-type KIT and wild-type PDGFRA regardless of the mutational status of any other gene). Randomization will be stratified by: • KIT exon 11 mutation; KIT exon 9 mutation; other (KIT/PDGFRA WT or other KIT [lacking exon 9 or 11]/PDGFRA mutation); The primary endpoint of the study will be evaluated using the modified Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1-GIST-specific based on independent radiologic review. Upon disease progression by RECIST v1.1-GIST-specific based on independent radiologic review, patients will discontinue their assigned treatment. Patients will be contacted by telephone 30 (±5) days after the last dose of the study drug for safety follow-up. After the end of the safety follow-up, survival follow-up visits will be made by phone every 2 month (±10 days).
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. Histological diagnosis of advanced GIST and capability of providing tumor tissue sample (the interval between tumor tissue collection and signing of informed consent form should be less than 3 years). Otherwise, biopsy is required. 3. Provide molecular test report with KIT/PDGFRA mutation status prior to randomization. Mutation status must be identified by tissue-based PCR or sequencing analysis. If molecular test report is not available or insufficient, biopsy of an archived tumor tissue sample or fresh tumor tissue is required for mutation status confirmation by the central laboratory prior to randomization. 4. Patients must have progressed on imatinib or have documented intolerance to imatinib. Subjects must have discontinued imatinib treatment 10 days prior to the first dose of the study drug. All prior imatinib treatments will be considered as first-line (such as imatinib adjuvant therapy and imatinib dose increase). 5. ECOG PS of 0-2. 6. Female patients of childbearing potential must have a negative serum beta-human chorionic gonadotropin (β-hCG) pregnancy test at screening. 7. Patients of reproductive potential must agree to follow the contraception requirements. 8. At least 1 measurable lesion according to the "RECIST v1.1-GIST-specific Criteria" (non-nodal lesions must be ≥1.0 cm in the long axis or ≥ double the slide thickness in the long axis) ; obtaining radiographic image results within 28 days prior to the first dose of study 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 • Creatinine clearance ≥ 50 mL/min (based on Cockcroft-Gault estimation Formulas for calculation) Note: Patients should receive no corrective treatment with granular colony stimulating factor or interleukin-11, infusion of red blood cells or platelets or other blood products within 2 weeks prior to detecting haematology. • Prothrombin time (PT), 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 study 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 study drug (excluding alopecia and ≤ Grade 3 clinically asymptomatic lipase, amylase, and creatine phosphokinase laboratory abnormalities). 11. Patient is capable of understanding and complying with the protocol. Subjects should sign the written informed consent before any study-related procedures were performed.
Exclusion criteria:	Subject meeting any of the following criteria should not be enrolled in this study: 1. Treatment with any other line of therapy in addition to imatinib for advanced GIST. Imatinib-containing combination therapy in the first-line treatment should not be enrolled. 2. Patients with a prior or concurrent malignancy whose natural history or treatment have the potential to interfere with the safety or efficacy assessment of this clinical trial are not eligible. For example, patients who received adjuvant treatment for cancer and used drugs which have potential activity to GIST or are prohibited by study protocol are not eligible. 3. Patient has known active central nervous system metastases. 4. New York Heart Association class II - IV heart disease, myocardial infarct, active ischemia or any other uncontrolled cardiac condition within the first 6 months of the first dose of study drug such as angina pectoris, clinically significant cardiac arrhythmia requiring therapy, uncontrolled hypertension or congestive heart failure. 5. Left ventricular ejection fraction (LVEF) < 50%. 6. Arterial thrombotic or embolic events such as cerebrovascular accident (including ischemic attacks) or hemoptysis within 6 months before the first dose of study drug. 7. Venous thrombotic events (e.g. deep vein thrombosis) or pulmonary arterial

	events (e.g. pulmonary embolism) within 1 month before the first dose of study drug. Patients on stable anticoagulation therapy for at least one month are eligible. 8. 12-lead electrocardiogram (ECG) demonstrating QT interval corrected by Fridericia's formula > 450 ms in males or > 470 ms in females at screening or history of long QT interval syndrome. 9. Use of strong or moderate inhibitors and/or inducers of cytochrome P450 (CYP) 3A4 within 14 days or 5 x the half-life (whichever is longer) prior to the first dose of study drug, including certain herbal medications (eg, St. John's Wort) and consumption of grapefruit or grapefruit juice within 14 days prior to the first dose of study drug. For CYP3A4 enzyme inhibition/induction-related drugs, please refer to the website of the Indiana University, School of Medicine (http://medicine.iupui.edu/clinpharm/ddis/main- table/). 10. Use of known substrates or inhibitors of breast cancer resistance protein (BCRP) transporters within 14 days or 5 x the half-life (whichever is longer) prior to the first dose of study drug. For information of inhibitors and substrates, please refer to Food and Drug Administration (FDA) website: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm. 11. Major surgeries (e.g. abdominal laparotomy) within 4 weeks of the first dose of study drug; all major surgical wounds must be healed and free of infection or dehiscence before the first dose of study drug. 12. Any other clinically significant comorbidities, such as uncontrolled pulmonary disease, active infection, or any other condition, which in the judgment of the investigator, could compromise compliance with the protocol, interfere with interpretation of the study results, or predispose the patient to safety risks. 13. Known human immunodeficiency virus or hepatitis C infection only if the patient is taking medications that are excluded per protocol, hepatitis B virus (HBV) DNA > 2000 IU/ml or > 10^4 copies/ml. 14. Female patients who are pregnant or lactating or who plan to become pregnant during the study treatment period. 15. Known hypersensitivity to any component of the study drug. Patients with Stevenson Johnson syndrome in previous TKI treatment need to be excluded. 16. Gastrointestinal abnormalities including but not limited to: • inability to take oral medication • malabsorption syndrome • Requiring intravenous nutrition 17. Any active hemorrhages, excluding hemorrhoids or gum bleeding.
Study drug	Drug of the test group: DCC-2618 (Ripretinib, ZL-2307) Dosage Form: Tablet Dosage: 150 mg QD continuous administration, 6 weeks (42 days) for a cycle. Administration route: oral Drug of the control group: Sunitinib Dosage form: capsule

	Dosage: 50 mg QD, in 6 weeks (42 days) with 4 weeks continuous dosing followed by 2 weeks break. Dose modifications are allowed per approved package insert. Administration route: oral
Study Endpoints	**Primary endpoints:** Progression-free survival (PFS):Independent radiologic review will assess PFS according to "RECIST v1.1-GIST-specific Criteria" which include: • No lymph nodes chosen as target lesions; enlarged lymph nodes will be followed as non-target lesions. • No bone lesions chosen as target lesions; • Positron emission tomography (PET) not acceptable for radiological evaluation; • A progressively growing new tumor nodule within a pre-existing tumor mass must meet the following criteria to be considered as unequivocal evidence of progression according to the modification of RECIST Version 1.1: (a) the lesion is at least 2 cm in size and definitively a new active GIST lesion (e.g. enhancing with contrast or other criteria to rule out artefact); or (b) the lesion has to be expanding on at least 2 sequential imaging studies. **Secondary endpoints:** **Efficacy Endpoints** • ORR (confirmed CR + confirmed PR) based on independent radiologic review • Disease control rate (DCR) at months 6, 9 and 12, assessed by independent radiologic review • PFS assessed by the investigator according to "RECIST v1.1-GIST-specific Criteria" • Overall survival (OS) **Safety:** • Incidence of treatment emergent adverse event (TEAE), adverse event of special interest (AESI) and serious adverse event (SAE); severity of adverse event will be assessed (based on NCI CTCAE 5.0); • Incidence of adverse events resulting in dose adjustment of the study drug or termination of the study; • Changes in each parameter like ECOG score, vital signs, electrocardiogram, left ventricular ejection fraction, dermatologic examination and laboratory indicators from baseline. **Pharmacokinetic profiles:** • Descriptive statistics and summary of drug concentration at relevant time points will be carried out according to plasma concentration of DCC-2618 (ripretinib, ZL-2307) after administration. If necessary, pharmacokinetic data of this study will be included into population PK analysis with industrial standard software. Population PK report will be drafted independently and not taken as the appendix of the study report. **Exploratory endpoint:** • KIT/PDGFRA mutation of tumor tissues at baseline and specific time

	points (e.g., resection of metastasis or progressive disease during the study). • KIT/PDGFRA mutations and mutant allele frequency at baseline and the treatment effect of DCC-2618 (ripretinib, ZL-2307) on KIT/PDGFRA mutant allele frequency (MAF).
Statistical analysis	Estimation of Sample Size: This study will bridge foreign clinical trial (study INTRIGUE) to prove the efficacy of the investigational drug DCC-2618 (ripretinib, ZL-2307) is consistent in foreign population and Chinese population. In the study, no statistical test hypothesis is specified in advance. Statistical significance test for efficacy endpoint and multiplicity correction for multiple analysis populations will not be performed. Approximately 98 subjects will be enrolled into the study and randomized to a test group and a control group in a 1:1 ratio. The sample size eatimation will be based on the same study hypothesis as foreign, that is, median progression-free survival (mPFS) is 9 months in the test group and 6 months in the control group. Hazard ratio (HR) of the test group to the control group is 0.667. If the study keeps ⩾50% of the overall effect size of study INTRIGUE, that is, point estimate of HR should be ⩽ 0.833, it will be considered that results of this study are consistent with those of study INTRIGUE. If 58 PFS events occur, the conclusion of consistency will be drawn with a probability of 80%. Assuming the subjects annual drop-out rate of the total study population is 5%, approximately 98 subjects (49 for the test group and the control group, respectively) are enrolled within 7 months and followed up for 7 months, and 58 PFS events will occur. Primary analysis based on ITT will be performed when 58 PFS events occur and it is estimated that the data cutoff of the analysis will be 7 months after completing enrollment. In population with KIT exon 11 mutation, it was assumed in the foreign study that mPFS of the test group was 9 months and mPFS of the control group was 5 months, and HR of the test group to the control group was 0.556. If the study keeps ⩾50% of the overall effect size of study INTRIGUE in population with KIT exon 11 mutation, that is, point estimate of HR should be ⩽ 0.778, it will be considered that results based on KIT exon 11 mutation population in this study are consistent with those in study INTRIGUE. If 26 PFS events occur in population with KIT exon 11 mutation, the conclusion of consistence with study INTRIGUE can be drawn with a probability of 80%. Note: If a patient has exon 11 mutation along with 1) exon 9 and/or PDGFRA mutation, the patient will be considered with exon 11 mutation at randomization. Mutation type of the patient will be defined according to a mutation with a higher MAF if the patient has mutation allele frequency (MAF) data; 2) other KIT exon mutation, the patient will be considered with exon 11 mutation at randomization.
Study duration	Patients will receive treatment until progressive disease confirmed by the independent radiologic review based on “RECIST v1.1-GIST-specific Criteria”, intolerable toxicity or withdrawal of consent. Patients will discontinue the study drug treatment if patients have progressive disease based on assessment of the independent radiologic review using

	"RECIST v1.1-GIST-specific Criteria". The longest medication duration of patients is 2 years. For patients with evidence of clinical benefit from the drug and tolerance to the drug and following the study procedure, the treatment duration will be prolonged by reaching an agreement between the sponsor and the investigator. The study will be terminated when the last patient has progressive disease or 20 months after finishing enrollment or when the sponsor determines to terminate the study, whichever occurs first.
Schedule of visits and the content thereof	Please refer to Table 1

Figure 1: Schematic diagram of the study

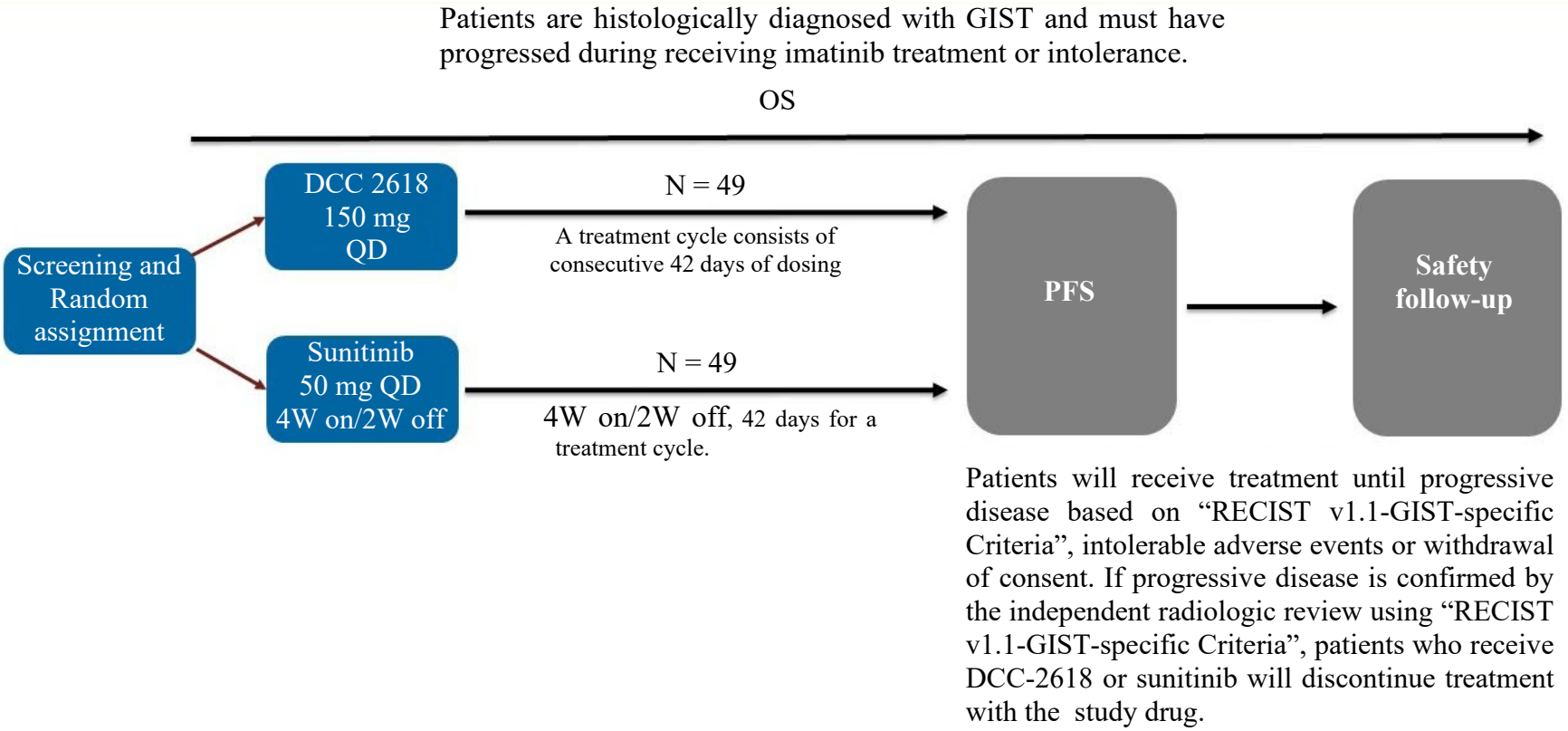

Table 1: Schedule of Assessments

Evaluation/Procedure[1]	**Screening** [2]	**Cycle 1**			**Cycle 2**		**≥ Cycle 3**	**EOT visit** (Within 7 days after the last dose)	**Safety follow-up**	**Overall survival follow-up**[3] (Every 2 month ± 10 days)
Cycle Day	**-28 to -1**	**1 (Baseline)**	**15** (± 1 day)	**29** (± 1 day)	**1** (± 3 day)	**29** (± 3 day)	**1** (± 3 day)		**Within 30 days after the last dose** (± 5 day)	
Come to the Study Site	X	X	X	X	X	X	X	X		
Tel									X	X
Informed consent	X									
Inclusion/Exclusion criteria	X									
Previous medical history and tumor history	X									
Previous medications/treatment[4]	X									
Pregnancy test[5]	X	X*			X		X	X		
Hepatitis B/C tests[6]	X						X	X		
HIV antibody test	X									
Clinical laboratory tests										
Blood routine	X	X*	X	X	X	X	X	X		
Blood biochemistry	X	X*	X	X	X	X	X	X		
Blood coagulation function[7]	X	X*	X	X	X	X	X	X		
Urine routine[8]	X	X*			X		X	X		
TSH, FT3 and FT4[9]	X	X*					X	X		
Physical examination	X	Examination will be arranged based on clinical findings and/or patients' chief complaints								
ECOG PS[10]	X	X*	X	X	X	X	X	X		
Vital signs and weight[11]	X	X*	X	X	X	X	X	X		
Height	X									
12-lead ECG[12]	X	X*			X		X	X		
Echocardiography/[13]	X						X	X		
Dermatologic examination[14]	X						X	X		

Evaluation/Procedure[1]	**Screening** [2]	**Cycle 1**			**Cycle 2**		**≥ Cycle 3**	**EOT visit** (Within 7 days after the last dose)	**Safety follow-up**	**Overall survival follow-up**[3] (Every 2 month ± 10 days)
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AEs reporting	Continuing from signing an ICF to the safety follow-up									
Concomitant medicines/other treatment		From the first dose of the study drug to safety follow-up								
Administration of study drug[15]		X	X	X	X	X	X			
Distribution and reconciliation of the study drug		X			X		X			
PK sampling[16]		X	X		X		X			
Molecular test report, marking KIT/PDGFRA mutation status[17]	X									
Archived tumor tissue sample/tumor biopsy [18]	X									
Optional tumor biopsy [19]								X		
Imageological examination[20]	X				X		X			
PD sampling (plasma) [21]		X						X		
Random assignment[22]		X								
Evaluate AE, collect information of concomitant medications/other treatments, collect information of new anti-tumor therapies									X	
Collect new information of anti-tumor therapy and OS data										X

CT = computerised tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; MRI = magnetic resonance imaging; PD = pharmacodynamic; PK = pharmacokinetic; PS = performance status

*: Examination with * doesn't need to be repeated on C1D1 if examination at screening is performed within 7 days prior to the first dose of the study drug.

1. Unless otherwise specified, all assessments must be carried out prior to administration and in the predetermined window of visit. Cycle is not influenced by suspension or delay of treatment with the study drug. Additional unscheduled safety or efficacy assessment can be carried out at any time with clinical indications to confirm the correlation between the specific findings and the study drug and/or duration of event. At unscheduled visits, if necessary, distribution and/or recovery of the study drug can be carried out.
2. Screening must be done within 28 days before the first dose of the study drug.
3. All patients will be followed up until withdrawal of consent or death for any reason. After safety follow-up visit, patients will be contacted once every 2 months (± 10 days) to collect new information of anti-tumor therapy and OS data.
4. Any medications or other therapies taken within 30 days prior to signing the informed consent form and prior to the first dose of the study drug.
5. A serum pregnancy test will be performed, at screening, for females of child-bearing potential. If serum pregnancy test at screening is performed within 7 days prior to the first dose of the study drug, urine pregnancy test is not required on C1D1. Urine pregnancy test will be carried out at visit of Day 1 of every subsequent cycle and EOT visit.
6. Hepatitis B and C examination: five indicators of hepatitis B and anti-HCV antibody examination will be performed at the screening period. If results of five indicators of hepatitis A are abnormal, HBV DNA quantitative test should be performed; if anti-HCV antibody positive, HCV RNA quantitative test should be performed. For patients with abnormal baseline HBV DNA, HBV DNA quantitative test should be performed once every 2 weeks during the trial and at the end of study. For patients with normal baseline HBV DNA, the test is not required during the trial.
7. For patients who take anticoagulant, the test should be performed on C1D15. If the dose of anticoagulant changes during the study, monitoring of coagulation function should be increased if clinically suitable.
8. Routine urine test will be performed at screening, on C1D1, C2D1, C3D1, C4D1, at EOT visit and when clinically necessary.
9. Serum TSH, FT3 and FT4 tests will be performed at screening, C1D1, Day 1 of every odd cycle (that is, Cycles 3, 5 and 7, etc.) and at EOT visit.
10. ECOG PS can be assessed before and after administration.
11. Measurements on vital signs must be collected at least 5 minutes after the patient has a rest (in a sitting or supine position).
12. All 12-lead ECG will be carried out at least 15 minutes after the patient has a rest.
13. Echocardiogram will be performed at screening, on C3D1 and Day 1 of every subsequent 3 cycles (that is, Cycles 6, 9 and 12, etc.) and at EOT visit or when clinically indicated. Echocardiogram as standard care before informed consent can be used for screening assessment as long as the echocardiogram is performed within 28 days prior to the first dose of the study drug.

14. For all patients, skin lesions will be assessed by a consultant dermatologist within 28 days (baseline) prior to C1D1, especially squamous cell carcinoma of skin, actinic keratosis and keratoacanthoma. After that, patients will receive assessment on C3D1, and Day 1 of every subsequent 3 cycles (that is, Cycles 6, 9 and 12, etc.), at EOT visit and when clinically necessary. Dermatologic examination meeting standard of the study protocol performed prior to informed consent can be used for screening evaluation as long as the examination is performed within 28 days prior to the first dose of the study drug. Dermatological examinations during the treatment period may be performed within at most 7 days before the corresponding follow-up visit or after the administration on the date of the follow-up visit. Please refer to Section 6.11.6 for further information.

15. On the date of study visit after finishing pre-dose evaluation, patients will be told to take the study drug at study site. Please refer to Section 5.3 for detailed information of dose and administration.

16. Only patients who use DCC-2618 (ripretinib, ZL-2307) will receive PK sampling at the following time points: before administration and 6 hours after administration on C1D1, before administration, 2 and 6 hours after administration on C1D15, and before administration on C2D1 and C3D1. All pre-dose samples must be collected within 60 minutes prior to administration and all post-dose samples must be collected within the specified time point ± 30 minutes. If the sponsor requires, unscheduled PK samples can be collected when new, suspicious, and treatment-related adverse events occur.

17. Molecular test report with KIT/PDGFRA mutation status must be provided. Mutation status must be identified by tissue-based PCR or sequencing analysis. Molecular test report with KIT/PDGFRA mutation status must be provided to the investigator before randomization so that the investigator can confirm randomization stratification factor. If molecular test report is not available or insufficient, biopsy of an archival tumor tissue sample or fresh tumor tissue is required for mutation status confirmation by the central laboratory prior to randomization.

18. In terms of collected archived tumor tissue samples, the central laboratory will analyze tumor tissues to identify molecular mutation of KIT or PDGFRA. Formalin-fixed paraffin-embedded tissue blocks (preferred) or unstained FFPE slices are required. If the archived tumor samples are unusable or inapplicable, new fresh tumor samples must be collected.

19. Tumor tissue samples can be collected at EOT visit from all patients (optional) and/or from patients who are receiving medical procedures, including resection of metastasis in the study, or from patients who have progressed (if the patient agrees). These samples will be used for further molecular test of cancer during receving the study drug.

20. Radiographic images must be done within 28 days before the first dose of the study drug. Radiographic examination prior to informed consent can be used for screening evaluation as long as the examination is performed within 28 days prior to the first dose of the study drug. Pelvic, abdominal and chest enhanced CT scan will be carried out at screening. During the study, pelvic and abdominal enhanced CT scan will be carried out on Day 1 of Cycles 2 - 7 and Day 1 of subsequent every odd cycle (such as Cycles 9, 11 and 13). If patients have lung metastases or symptoms of lung metastases at screening and during the study, chest CT enhanced scan should be performed (at the investigator’s discretion). Radiographic images can be performed within the corresponding study visit ±

7 days. After C7D1, based on the investigator's assessment, any initially indicated partial or complete response should be confirmed ≥ 4 weeks after the start of response. MRI scans of the abdomen/pelvis and CT scan without contrast of the chest can be used for patients who are allergic to radiographic contrast media or at the Investigator's discretion based on the best interest of the patient after discussion with the Sponsor. For each patient, the same evaluation technology should be adopted during the whole study, and the evaluation technology could not be changed unless the investigator's consideration of safety risk. Ultrasound scan should not replace CT scan.

Validation of progressive disease: if the independent radiologic review considers there is no progressive disease based on "RECIST v1.1-GIST-specific Criteria", the patient will continue receiving the study drug, unless the study drug should be discontinued for medical need (that is, fast progression or clinical worsening). If investigators confirm progression according to clinical worsening, radiographic images should be performed and reviewed by independent radiologic institutions to confirm whether the patient has progression. The basis of confirming progression according to clinical worsening must be recorded in source data and electronic case report form of patients. If the investigator confirms progressive disease according to "RECIST v1.1-GIST-specific Criteria", the investigator should wait for confirmation by the independent radiologic review and then terminate the patient's treatment. If the investigator doesn't hope to confirm by the independent radiologic review or hopes to terminate the patient's treatment according to progressive disease based on "RECIST v1.1-GIST-specific Criteria" before obtaining results of the independent radiologic review, it is necessary to discuss with the sponsor. Radiographic examination of patients of various treatment groups should be performed according to the predetermined time and cycle will not be influenced by suspension or delay of treatment with the study drug. If the patient discontinues treatment for reasons other than progressive disease, death, withdrawal of consent and lost to follow-up, the patient should receive radiographic examination for tumor assessment according to the specified time interval after treatment withdrawal until progressive disease based on "RECIST v1.1-GIST-specific Criteria" or initiation of new anti-tumor therapy.

21. Blood samples of patients who use DCC-2618 (ripretinib, ZL-2307) and sunitinib will be collected within 60 minutes prior to administration on C1D1 (baseline), and when the independent radiologic review confirms progressive disease according to "RECIST v1.1-GIST-specific Criteria" or at EOT visit.

22. Randomization can be carried out on Day -1. Patients who will be randomized on C1D1 can be randomized on the former Friday.

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LIST OF ABBREVIATIONS

List of Abbreviations	Definition
AE	AEs
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
ASM	Aggressive systemic mastocytosis
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the time-concentration curve
AUC_{0-24}	24-Hour area under the time-concentration curve
β-hCG	β-human chorionic gonadotropin
BCRP	Breast cancer resistance protein
BID	Twice daily
BP	Blood pressure
BSEP	Bile salt export pump
cfDNA	Cell-free DNA
C_{max}	Observed maximum concentration
CPK	Creatine phosphokinase
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CYP	Cytochrome P450
DCR	Disease control rate
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOT	End of treatment
ER	Excretion rate
FDA	Food and Drug Administration
FFPE	Formalin-fixed, paraffin-embedded
FSH	Follicle stimulating hormone
FT3	Tri-iodothyronine free
FT4	Thyroxine free
fu	Free fraction
GCP	Good Clinical Practice
GI	Gastrointestinal
GIST	Gastrointestinal stromal tumor
GLP	Good Laboratory Practice

List of Abbreviations	Definition
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDPE	High-density polyethylene
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independence Ethics Committee
IC_{50}	Half maximal inhibitory concentration
INR	International Normalized Ratio
IRB	Institutional Review Board
IRR	Independent Radiologic Review
ITT	Intent-to-treat
IV	Intravenous
KM	Kaplan-Meier
LHRH	Luteinizing Hormone-Releasing Hormon
LVEF	Left ventricular ejection fraction
MAF	Mutation allele frequency
MDR1	Multidrug Resistance Protein 1
MedDRA	Medical Dictionary for Regulatory Activities
mPFS	Median progression-free survival
MRI	Magnetic Resonance Imaging
MTD	Maximum tolerated dose
NADPH	Nicotinamide adenine dinucleotide phosphate
NCI	National Cancer Institute
NOAEL	No observed adverse effect level
OAT	Organic anoin transporter
OCT	Organic cation transporter
ORR	Object Response Rate
OS	Overall survival
PD	Pharmacodynamics
PET	Positron Emission Tomography
PFS	Progression-free survival
PK	Pharmacokinetics
PP	Per Protocol
PR	Partial response
PS	Performance Status
PT	Pro-thrombin Time
PTT	Partial thromboplastin time
QD	Once daily
QTc	Corrected QT interval
QTcB	QT interval corrected by Bazett's formula

List of Abbreviations	Definition
QTcF	QT interval corrected byFridericia's formula
RECIST	Response Evaluation Criteria In Solid Tumours
RP2D	Recommended Phase 2 dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCC	(Skin) Squamous Cell Carcinoma
SD	Stable Disease
SJS	Stevens-Johnson syndrome
SM	Systemic Mastocytosis
SOC	System organ class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
T_{max}	Observed maximum concentration
TSH	Thyroid Stimulating Hormone
$T_{1/2}$	Half-life
ULN	Upper limit of normal
WT	Wild type

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1. Introductionand Basic principles

1.1. Introduction

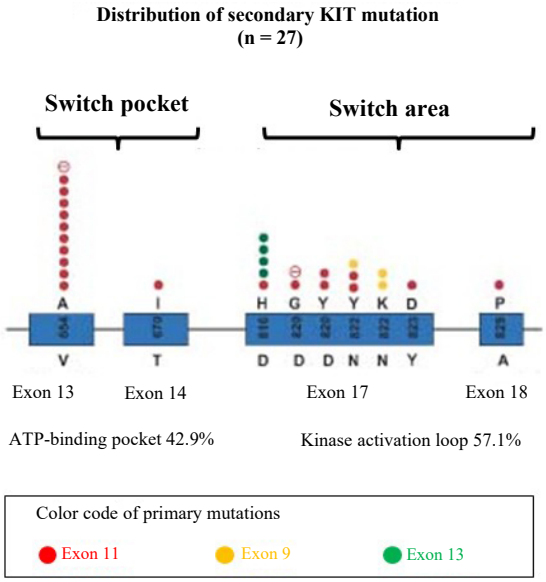
Studies revealed that activating mutation of KIT or PDGFRA of receptor tyrosine kinase exists in many cancers such as gastrointestinal stromal tumor (GIST), melanoma subtype, seminoma of testis and acute myeloid leukemia (AML) as well as myeloproliferative neoplasm such as systemic mastocytosis (SM) including aggressive systemic mastocytosis (ASM) and mast cell leukemia[1,2,3, 4,5]. Studies also revealed that GIST, melanoma, AML, glioma and neuroendocrine tumor presented abnormal wild-type KIT and/or PDGFRA over-expression[6,7,8,9].

Most GIST is induced by activated mutation in KIT (about 80%) or relevant PDGFRA (about 10%) receptor tyrosine kinase[11,300]. In GIST patients, exon 9 or 11 mutations are the most common in KIT mutation. 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 treatment, secondary drug-resistant KIT mutation generally occurs in the catalytic domain of kinase and these mutations are usually reflected in embedded conformational switch control mechanism that regulates KIT activity (

Figure 2) Secondary KIT mutations usually occur in exons 13 and 14 (approaching adenosine triphosphatase [ATP]-binding 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[10,11]. Activation loop mutation can transform kinase into activation conformation, making it difficult to bind to the approved therapeutic drugs[12]. Other diseases harboring primary KIT (or PDGFRA) activation loop mutations include SM, AML and PDGFRA-induced GIST[6,13,14].

Figure 2: Various secondary KIT mutations in cross-exon 13 - 18 in GIST patients



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

Imatinib is the first KIT inhibitor and was approved in 2002 for the treatment of advanced GIST [15]. Imatinib generally cannot cure unresectable and/or metastatic diseases and its complete response rate (CR) was about 5% and objective response rate (ORR) was 68% [16]. Over 80% of GIST patients obtained clinical benefit from imatinib monotherapy. However, imatinib resistance was basically unavoidable for patients and over half of patients had progressive disease within 2 years[17]. The main cause for progression was secondary KIT kinase mutation, inducing resistance to imatinib [11]. Although imatinib can effectively inhibit exon 11 mutation in KIT and dose increase to 800 mg was effective to exon 9 mutation, imatinib doesn't or almost doesn't have inhibitory effect on KIT and PDGFRA mutation, especially on mutations of conformation dynamic mediating switch activation [17, 18].

In 2006, sunitinib was approved as second-line therapy in GIST patients who have progressed after imatinib treatment or are intolerant to imatinib. Sunitinib has a stronger inhibitory effect on exon 9 mutation than imatinib and a weaker inhibitory effect on exon 11 mutation [14, 17]. In addition, sunitinib presented anti-tumor activity to KIT exons 13 and 14 mutations, but only half of the patients benefited from it, with a median progression-free survival (PFS) of 5.5 months[17]. Sunitinib was ineffective in patients with KIT exons 17/18 mutations and PDGFRA exon 18 mutation r in the activation loop.

Regorafenib was approved as third-line therapy in 2013 in adult patients with metastatic and/or unresectable GIST who have progressed after receiving imatinib and sunitinib treatment or are not tolerant to imatinib and sunitinib. Besides inhibitory activity to KIT exon 11 mutation, regorafenib is the only approved therapy with an inhibitory activity to KIT exon 17 mutation subtype. For patients responding to regorafenib, PFS was nearly 5 months. Regorafenib cannot effectively treat some patient with KIT mutation. In such case, these patients may have other

or multiple secondary mutations, leading to resistance to regorafenib [11]. Studies showed that for an individual patient, tumor heterogeneity and multiple secondary KIT mutations were observed in different regions of a tumor or different metastatic sites [11].

Complex heterogeneity of KIT mutation in individual patient is a main cause for drug resistance [11]. Kinase inhibitor that can extensively inhibit clinical KIT mutation or multiple KIT mutation in individual GIST patients has a high treatment value for refractory GIST patients. What's more, it is an important treatment objective to confirm whether DCC-2618(Ripretinib, ZL-2307) can delay the occurrence of KIT mutations leading to drug resistance.

At present, no kinase inhibitor that can extensively inhibit secondary drug-resistant mutation in GIST patients has been marketed. Therefore, it is urgent to develop kinase inhibitor that can effectively inhibit multiple KIT and PDGFRA mutations.

1.2. Clinical Indications

DCC-2618 (ripretinib, ZL-2307) is a KIT and PDGFRA kinase inhibitor. At present, the drug is under development and expected to treat GIST and other advanced malignant tumors induced by proto-oncogene tyrosine protein kinase. DCC-2618 can not only inhibit KIT and PDGFRA but also inhibit CSF1R (FMS), VEGFR2 and TIE2. According to literatures, these substances seldom induce tumor progression, but are associated with tumor growth.

GIST is the most common type of sarcoma, formed in human mesenchymal cells but is a relatively rare cancer subtype [19]. There are approximately 3000 - 6000 new GIST patients every year in America [20, 21, 22] and the age of onset is usually 50 - 70 years, with a similar prevalence in males and females [23]. Surgery, as the main treatment for local GIST, can realize a radical effect, but over half of patients had local and/or distant metastasis [24]. Approximately half of patients had metastatic or unresectable GIST, while radiotherapy and traditional chemotherapy are ineffective in these patients [19, 24]. In the era of targeted cancer therapy, several new effective therapies have been developed for metastatic and recurrent GIST though CR is seldom reached [19]. Most patients have resistance to treatment within several months to years depending on treatment method [20], which is similar to result observed in targeted therapy of other tumors.

1.3. DCC-2618 (Ripretinib, ZL-2307)

DCC-2618 (Ripretinib, ZL-2307) is a new orally administered KIT kinase and PDGFRA kinase inhibitor developed by Deciphera Pharmaceuticals, LLC (thereafter refer to "the Sponsor") using its special kinase switch control inhibitor technological platform. DCC-2618 (Ripretinib, ZL-2307) can comprehensively and potently inhibit extensive primary and secondary KIT and PDGFRA kinase mutants, including primary KIT 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

(Ripretinib, ZL-2307) 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 (Ripretinib, ZL-2307), as an enhanced type II kinase inhibitor, penetrates embedded KIT/PDGFRA switch pocket by binding to extensively inhibit KIT/PDGFRA mutants.

1.3.1. Nonclinical Experience

Please refer to Investigator's Brochure (IB) for more details of summary of non-clinical experience of DCC-2618 (ripretinib, ZL-2307).

1.3.1.1. Pharmacology

Recombinant kinase test and cell test were carried out with drug-resistant cell lines of GIST patients, AML and mastocytosis or cell lines transfected with KIT or PDGFRA mutants, so as to conduct in vitro active evaluation of DCC-2618 (Ripretinib, ZL-2307) and its active metabolite DP-5439. The above study revealed that DCC-2618 (Ripretinib, ZL-2307) can comprehensively inhibit clinically significant KIT and PDGFRA mutations that can't be treated with or don't respond to current therapies. Evaluation results of cancer cell lines provide guidance for further evaluation of DCC-2618 (ripretinib, ZL-2307) in refractory/drug-resistant in vivo xenograft model.

Multiple cancer model systems were adopted for in vivo pharmacological evaluation of DCC-2618 (ripretinib, ZL-2307), including efficacy assessment in human tumor xenograft nude mouse model and study of pharmacokinetic (PD)/pharmacodynamic (PD) in tumor-bearing mice, so as to evaluate exposure of drug required for persistent inhibition of KIT mutation in vivo.

DCC-2618 (ripretinib, ZL-2307) showed a potent in vivo anti-tumor effect in KIT mutation GIST model. Moreover, DCC-2618 (Ripretinib, ZL-2307) can also effectively inhibit KIT phosphorylation in GIST model. DCC-2618 (ripretinib, ZL-2307) can also inhibit tumor growth in HMC1.2 (exon 11 V560D and exon 17 D816V double mutation) mastocytosis xenograft model and presented a potent inhibitory effect in H1703 lung cancer xenograft model with PDGFRA amplification.

A PK/PD study in human GIST xenograft model in mice indicated that after a single dose of 50 mg/kg, exposure (0-24 hour area under the time-concentration curve [$AUC_{0\text{-}24hr}$]) of DCC-2618 (Ripretinib, ZL-2307) was 2500 ng•h/mL (including after active metabolite DP-5439, exposure was 5000 ng•h/mL); inhibition rate against KIT was 69-88% within 8 hours after administration and about 40% 12 hours after administration. In a multiple-dose efficacy study, when administering at 50 mg/kg twice daily (BID, daily exposure 10,000 ng•h/mL) to GIST T1 model, inhibition rate of the drug exposure to tumor growth was 90%. This PK/PD-derived exposure is used to guide the identification of toxicological products that can realize several times that of the exposure persistently inhibiting KIT in vivo.

Hepatocellular metabolite identification study indicated that the main metabolic pathway of

DCC-2618 (Ripretinib, ZL-2307) is an active metabolite named DP-5439 formed by N-demethylation. In preclinical studies in animals, effective dose 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-2618 (Ripretinib, ZL-2307) exposure in mice was equivalent to DCC-5439 exposure. Total exposure ($AUC_{0\text{-}24hr}$) of active drug in mice was calculated by determining the total exposure of DCC-2618 (ripretinib, ZL-2307) and its metabolite DP-5439, that is, exposure was 5000 ng•h/mL after a single oral dose of 50 mg or 10,000 ng•h/mL after administration at 50 mg/kg BID. This value will be taken as reference value in non-clinical safety study. A phase 1 ascending dose study also confirmed that metabolite DP-5439 will form. At a clinically effective dose, exposure of metabolite was higher than original DCC-2618 (Ripretinib, ZL-2307) exposure.

Efficacy and tolerability observed in these model systems choose the clinical development of DCC-2618 (Ripretinib, ZL-2307).

1.3.1.1.1. Safety pharmacology

Binding of DCC-2618 (Ripretinib, ZL-2307) to human ether-à-go-go related gene potassium channel components can be ignored.

DCC-2618 (Ripretinib, ZL-2307) 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. DCC-2618 (Ripretinib, ZL-2307) at 15, 60 or 300 mg/kg was administered to rats. 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 and 13-week repeat-dose toxicological study was carried out in dogs, and cardiovascular safety was assessed by measuring their electrocardiogram (ECG), blood pressure (BP) and troponin I levels. The study drug did not have significant impact on BP, heart rate, ECG intervals and troponin I level. In an independent cardiovascular safety study, after the investigator gave a single dose of DCC-2618 (Ripretinib, ZL-2307) to telemetered Beagle dogs, both 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 (Time to observed maximum concentration [T_{max}]). At doses of 7, 20 and 75 mg/kg, diastolic blood pressure was higher than that of the control group (higher by 12, 12 and 17%, respectively). At doses of 7, 20 and 75 mg/kg of DCC-2618 (ripretinib, ZL-2307), the mean arterial pressure was higher than that in the control group (higher by 12, 10 and 14 mmHg, respectively). Systolic blood pressure or arterial pressure didn't change.

In the dark 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). The corrected QT interval (QTc) didn't change. In the whole dark 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; BP and heart rate will be closely monitored in the clinical study. Although the change pace of BP and heart rate is more significant, this does not mean the study drug has severe toxicity.

1.3.1.2. Pharmacokinetics and characteristics of absorption, distribution, metabolism and excretion

In vitro studies were carried out in human and other drug development-related mammal species to confirm absorption, distribution, metabolism and excretion characteristics of DCC-2618 (Ripretinib, ZL-2307) and its active metabolite DP-5439. In vivo PK studies (the administration routes are oral and intravenous injection [IV]) were carried out in rodents (mice and rats) and non-rodents (dogs and cynomolgus monkeys). When administered orally, bioavailability of DCC-2618 (ripretinib, ZL-2307) was highest in all species, proving its development potential as an oral drug.

Total exposure ($AUC_{0\text{-}24hr}$) of DCC-2618 (ripretinib, ZL-2307) in dogs and rats was 1.9 - 2.6 times target area under the curve (AUC) 10,000 ng•h/mL of DCC-2618 (ripretinib, ZL-2307) and metabolite DP-5439 in mice GIST efficacy model. Dogs and rats were given a single IV dose, and half-life time ($T_{1/2}$) 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 metabolite in liver cells of all species was N-demethylation metabolite (DP-5439). Accordingly, it can be confirmed that DP-5439 could inhibit KIT and PDGFRA wild type and mutation and has an equivalent potency to DCC-2618 (ripretinib, ZL-2307). In testing of 19 single and double KIT mutants conducted in transfected Chinese Hamster Ovary Cells, the result showed that DCC-2618 (Ripretinib, ZL-2307) inhibited phosphorylation of mutant KIT, with median maximum inhibition concentration (IC50) between 6 nM - 221 nM These studies revealed that DP-5439 can also inhibit phosphorylation of KIT mutant and its IC_{50} ranged 21 - 191 nM.

In vitro metabolism of DCC-2618 (Ripretinib, ZL-2307) and active metabolite DP-5439 by human liver microsome was studied to confirm which human cytochrome P450 (CYP) is conducive to DCC-2618 (Ripretinib, ZL-2307) metabolism. Studies showed that metabolism of DCC-2618 (ripretinib, ZL-2307) should be carried out in the presence of reduced nicotinamide adenine dinucleotide phosphate (NADPH). In the cultured human liver microsomes, combination of specific direct CYP inhibitor or metabolism-dependent CYP inhibitor was used to block metabolism of DCC-2618 (ripretinib, ZL-2307). Results showed that CYP3A4/5 was the main metabolic enzyme (ketoconazole inhibition rate 63%; troleandomycin inhibition rate 79%) of DCC-2618 (ripretinib, ZL-2307), while CYP2C8 (glucuronic acid of gemfibrozil inhibition rate 24%) and CYP2D6 (quinidine inhibition rate

26%) were secondary metabolic enzymes. However,the study also found that, in recombinant human CYP enzyme products, CYP2D6 and CYP2C8 were potent metabolic enzymes of DCC-2618 (Ripretinib, ZL-2307). Inhibition to DP-5439 was observed in microsome incubated by the following inhibitors, which include: direct inhibitor ketoconazole (CYP3A4/5, 72% inhibition), metabolism-dependent inhibitor gemfibrozil-glucuronic acid (CYP2C8, 59% inhibition), tienilic acid (CYP2C9, 25% inhibition), esomeprazole (CYP2C19, 31% inhibition), paroxetine (CYP2D6, 42% inhibition), diethyldithiocarbamate (CYP2E1, 50% inhibition) and troleandomycin (CYP3A4/5, 100% inhibition) . When DP-5439 and other direct or metabolism-dependent inhibitors were incubated together, the estimate result showed that inhibition rate was lower than 14%. The study indicated that metabolite DP-5439 was mainly metabolized through CYP3A4/5, but CYP2C8, CYP2E1 and CYP2D6 may also promote significant metabolism. In an in vitro metabolism study, DCC-2618 (ripretinib, ZL-2307) didn't obviously inhibit CYP3A4, CYP1A2 or CYP2B6. IC_{50} of DCC-2618 (Ripretinib, ZL-2307) in inhibiting CYP2C8, CYP2C9, CYP2C19 and CYP2D6 ranged 0.12 - 1.8 μM. Of the assessed 7 main CYP enzymes, inhibitory effect of DCC-2618 (ripretinib, ZL-2307) was unrelated or almost unrelated to time or metabolism.

IC_{50} of metabolite DCC-5439 in inhibiting CYP2C8, CYP2C9, CYP2C19 and CYP2D6 ranged 0.30 - 2.0 μM. DP-5439 did not significantly and directly inhibit CYP3A4, CYP1A2 or CYP2B6. However, after incubating together with human liver microsome for 30 minutes in the presence of NADPH, DP-5439 had metabolism-dependent (time-dependent and NADPH-dependent) inhibitory effect on CYP3A4/5-mediated testosterone 6β-hydroxylation. After preincubate, inhibition rate of DP-5439 increased by 41% at a concentration of 7.0 μM. DP-5439 has little or none metabolism-dependent (time-dependent and NADPH-dependent) inhibitory effect on CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP2D6. When DCC-2618 (ripretinib, ZL-2307) and DP-5439 are combined with other drugs inhibiting CYP2C8, CYP2C9, CYP2C19 or CYP2D6, DDI may occur during metabolism, which is dependent upon the drug.

In the presence of 10 μM DCC-2618 (Ripretinib, ZL-2307) or 7 μM DP-5439, organic anion transporter (OAT) OAT1 and OAT3, organic cation transporter (OCT) OCT1 and OCT2 were mildly or moderately inhibited, with inhibition ≤ 55%. Inhibition rate of DCC-2618 (Ripretinib, ZL-2307) 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 (Ripretinib, ZL-2307) and DP-5439 inhibited efflux transporter breast cancer resistance protein (BCRP), and IC_{50} was 0.04 μM and 1.26 μM, respectively. Although DCC-2618 (ripretinib, ZL-2307) is not the substrate of BCRP transporter (excretion rate [E] is 2.36), metabolite DP-5439 shows a significant substrate activity (ER os 85.0), indicating the drug may interact with metabolite. DCC-2618 (ripretinib, ZL-2307) may be the substance (BCRP IC_{50} is 0.04 μM) inducing drug interaction, while metabolite DP-5439 may be a substance (BCRP ER is 85.0) influenced by drug interaction. DCC-2618 (Ripretinib, ZL-2307) may also have drug interaction with

substrate or inhibitor as other BCRP efflux transporters.

DCC-2618 (Ripretinib, ZL-2307) and DP-5439 had a moderate to weak inhibitory effect on multidrug resistance efflux transporter 1 (MDR1), and IC_{50} was 1.95 μM and > 7 μM, respectively. Although DCC-2618 (Ripretinib, ZL-2307) 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 (Ripretinib, ZL-2307) was likely to be the substance inducing interaction (MDR1 IC_{50} 1.95 μM), and metabolite DP-5439 may be a substance (MDR1 ER 72.4) (Table 2).

Table 2: Interaction between DCC-2618 (Ripretinib, ZL-2307) and transporters of its metabolite DP-5439

	Inhibition on 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
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

IC_{50} = median maximum inhibition concentration; ER = excretion rate; NT = not tested; BSEP = bile salt export pump

1.3.1.3. Toxicology

Toxicological characteristics of DCC-2618 (Ripretinib, ZL-2307) were assessed in vivo and in vitro bacterial mutagenicity analysis in nude mice, Sprague-Dawley rats and Beagle. In an assessment per Good Laboratory Practice, at the maximum testing concentration 3000 μg/plate (concentration at which precipitation was formed) in a bacterial mutagenicity test, regardless of metabolic activation, no clear bacterial mutagenicity was observed.

In a critical, per-GLP 4-week oral study in rats, DCC-2618 (ripretinib, ZL-2307) was administered at 0, 15, 60 and 300 mg/kg.day. After administration, animals in the observation period were observed for 4 more weeks. No drug-related death or adverse clinical observation result was reported in this study. Incidence of hair thinning at the dose of 300 mg/kg/day was higher. In animals treated with DCC-2618 (ripretinib, ZL-2307), weight decrease and food consumption decrease were observed. Body weight and food consumption change was reversed

in the recovery period and the drug didn't have any influence on the overall physical status of animals. Several mild clinical pathological findings were observed on Day 29. These changes were very minor, were not clinically relevant under microscopy and reversible at the end of the recovery period. Therefore, these changes were not considered as adverse reactions. DCC-2618 (ripretinib, ZL-2307)-related lung weight increase (15 - 33%) was observed in male rats in the 300 mg/kg/day dose group and female rats in dose ≥ 15 mg/kg/day group There was no related microscopic change and lung weight increase was partially reversed during the recovery period. Micro-changes in non-glandular stomach (diffuse hyperplasia/hyperkeratosis) were observed in rats receiving treatment at ≥ 60 mg/kg/day and some of these changes were reversible in the recovery period. This kind of change was unrelated to human because human do not have the anatomical feature. According to these results, no observed adverse effect level (NOAEL) after 4-week administration was 300 mg/kg/day.

In a 13-week per-GLP study, 30, 100 and 300 mg/kg/day DCC-2618 was given to Sprague Dawley rats by oral administration. The study revealed that rats had growing incisor teeth loss/discolouration (only 300 mg/kg/day group), skin discoloration and skin lesion (dose ≥ 30 mg/kg/day group), hair loss or thinning, weight and weight gain decrease, and food consumption decrease (only female rats in the 300 mg/kg/day group). Clinical observation showed that three rats (one from the main study and two from toxicokinetics study) in the 300 mg/kg/day group had skin lesions and were killed in an unscheduled period for humanity. Clinical pathological findings were consistent with inflammation and/or stress response and related to skin changes. Liver enzyme activity increased was related to changes in liver portal veins. Microscopic findings indicated degradation of incisor teeth and proximal duodenum Brunner's gland in female rats in the 300 mg/kg/day group, testis degeneration/atrophy and epididymis cell debris increased in male rats in the 300 mg/kg/day group.The above events were severe enough to consider them as adverse events. Therefore, NOAEL of DCC-2618 (ripretinib, ZL-2307) was 100 mg/kg/day. Exposure (observed maximum concentration [C_{max}] and AUC) of DCC-2618 (ripretinib, ZL-2307) and DP-5439 on Day 1 was about twice as much as that on Day 91. In the 13-week administration period, the most obvious skin changes were observed in an early stage.

In a critical, per-GLP 4-week oral study in beagles, doses were 0, 7, 20 and 75 mg/kg/day. After administration, animals in the observation period were observed for 4 more weeks. Due to adverse clinical observation results related to DCC-2618 (ripretinib, ZL-2307), the drug was discontinued in several animals using the drug at 20 and 75 mg/kg/day at weeks 2 and 3. Due to adverse clinical observation results related to DCC-2618 (ripretinib, ZL-2307), three male dogs in the 75 mg/kg/day group were killed on Day 13 and another 7 dogs in the 20 mg/kg dose group (2 males and 2 females) and 75 mg/kg dose group (3 females) were killed at week 4 in advance. The clinical observation results of these animals included, erythema in foot, ears, nose, mouth, periorbital area and on ventral chest, and head hair thinning. Some test animals had skin dryness and crack, otitis, external auditory canal erythema, excessive drooling,

vomiting and fecal formlessness/liquid feces. In test dogs in the 7 mg/kg/day dose group, skin changes were observed, but the severity was mild. Therefore, the changes were not considered as adverse reactions. Skin lesion in the 20 and 75 mg/kg/day dose groups partially or completely resolved in the recovery period. Weight decrease was observed in male dogs in 20 and 75 mg/kg/day dose groups. Body weight change of animals in the 7 mg/kg/day group was minor and not considered as adverse reaction. In any dose group of DCC-2618 (ripretinib, ZL-2307), no BP or ECG interval change was observed. In animals of dose ≥ 20 mg/kg/day group, mild hematological, clinical biochemical and/or coagulation abnormalities were observed and there was evidence that these changes were reversed after the recovery period. In animals treated with DCC-2618 (ripretinib, ZL-2307), troponin I level was not influenced by drug therapy. When the administration dose ≥20 mg/kg/day, hyperkeratoses, sparse cytoplasm of liver cells (consistent with glycogen increased), lymphocytes decreased in lymphoid tissues and one case of intraepithelial pustule were observed in microscopy. In some animals in the 75 mg/kg/day dose group, the only test product-related microscopic finding when killing animals in the recovery period was very mild sparse hepatic cytoplasm, indicating it was recovered in some animals.

On the basis of these results, NOAEL was 7 mg/kg/day. The dose was also considered as the highest non-severely toxic dose.

In a 13-week per-GLP study, 2.5, 5 and 10 mg/kg/day DCC-2618 was given to beagles daily and it was found that skin damage, hair thinning/loss were observed in all dose groups. When the dose ≥ 5 mg/kg/day, skin sensation of warmth was observed. For adverse skin damage in the 10 mg/kg/day group, interventional measures such as non-steroidal anti-inflammatory drugs (NSAID) and antibiotics were given from week 6 of the administration period to terminal autopsy. Clinical pathological findings were consistent with inflammation and/or stress response. Microscopic findings of skin hyperplasia/hyperkeratosis were consistent with clinically observed skin damages. One female animal in the 10 mg/kg/day group had poor domestication and obvious weight decrease prior to the first dose of the test product. Nevertheless, it was still believed that DCC-2618 (ripretinib, ZL-2307) induced physical decline of the female rat and study of the animal was terminated prematurely. Therefore, NOAEL of DCC-2618 (ripretinib, ZL-2307) was 5 mg/kg/day after 13-week administration.

1.3.2. Clinical Experience

American IND 125279 became effective in 2015 to support clinical development of ripretinib in KIT/PDGFRA-driven malignant tumors.

First-in-human (FIH) study DCC-2618-01-001 is a phase 1, open-label, dose-escalation and expansion study conducted in patients with advanced malignant tumors. The primary objective of this study is to confirm the maximum tolerated dose (MTD) of DCC-2618 (Ripretinib, ZL-2307) and to assess its safety, tolerability, preliminary efficacy, PK and PD effect. Data in the dose-escalation period in the FIH study support to select 150 mg QD as the recommended

phase 2 dose (RP2D). Extension period of the study was initiated in the middle of 2017 and the drug was administered at RP2D. As of March 1, 2019, a total of 237 patients were enrolled into the dose-escalation and extension period of the study and 181 patients (12 in the dose-escalation period and 169 in the extension period) took RP2D 150 mg QD as the starting dose. In addition, 142 patients were diagnosed with advanced GIST.

Another ongoing phase 3 registration study (DCC-2618-03-001; INVICTUS) is a randomized, double-blinded, placebo-controlled study in advanced GIST patients who have previously received imatinib, sunitinib and regorafenib treatment. The study was initiated in January 2018. Enrollment (N=129) of this study was finished in November 2018 and the primary endpoint was progression-free survival (PFS). The number of PFS events required for the planned analysis of the study was 90 and was reached in May 2019. Deciphera submitted NDA in December 2019 to seek complete approval because the study had reached its primary endpoint based on final analysis results. On May 15, 2020, the FDA approved ripretinib for adult patients with advanced GIST who have received prior treatment with three or more kinase inhibitors, including imatinib. In June and July, 2020, ripretinib was also approved for fourth-line GIST in Canada and Australia respectively.

1.3.2.1. Clinical Safety

1.3.2.1.1. Overview

Because study DCC-2618-01-001 is ongoing, only source of some clinical data may not be validated or proved. Therefore, there may be changes. The data represent the latest formal cut-off data of the study.

As of March 1, 2019, a total of 237 patients received (DCC-2618 (ripretinib, ZL-2307) treatment, 181 (12 in the dose-escalation period and 169 in the extension period) of whom took RP2D 150 mg QD as the starting dose, and 142 of whom were diagnosed with advanced GIST.

The following

Table 3 lists safety data (TEAE with an incidence ≥ 10% in GIST patients in the 150 mg QD dose group) of GIST patients (N = 142) receiving 150 mg QD treatment.

In general, DCC-2618 (ripretinib, ZL-2307) has a good tolerability and treatment-related serious adverse event (SAE) and grades 3/4 event was seldom reported.

Not captured in Table 3, is a Grade 3 (severe) SAE of Stevens-Johnson syndrome (SJS)/hypersensitivity reaction. The event was reported as SJS in a 38-year-old Asian female 10 days following the initiation of ripretinib in the Phase I (FIH) study. After a positive re-challenge at a reduced dose, the study treatment was permanently discontinued due to the event and the event resolved on Day 51 of the study. A Grade 3 SJS corresponds to skin sloughing covering <10% of body surface area. It was considered related to DCC-2618. If a patient experiences SJS/hypersensitivity reaction while being treated with DCC-2618, DCC-2618 must be permanently discontinued.

Table 3: TEAE with an incidence ≥ 10% at a dose of 150 mg QD (n = 142)

Preferred term	Second-line (N=31) n (%)	Third-line (N=28) n (%)	Fourth-line (N = 46) n (%)	> Fourth-line (N = 37) n (%)	≥ Fourth-line (N = 83) n (%)	Total GIST patients (N = 142) n (%)
Any event	31 (100.0)	28 (100.0)	46 (100.0)	37 (100.0)	83 (100.0)	142 (100.0)
Alopecia	22 (71.0)	21 (75.0)	23 (50.0)	19 (51.4)	42 (50.6)	85 (59.9)
Fatigue	20 (64.5)	15 (53.6)	25 (54.3)	16 (43.2)	41 (49.4)	76 (53.5)
Myalgia	15 (48.4)	16 (57.1)	20 (43.5)	16 (43.2)	36 (43.4)	67 (47.2)
Nausea	14 (45.2)	15 (53.6)	16 (34.8)	18 (48.6)	34 (41.0)	63 (44.4)
Palmar-plantar erythrodysesthesia syndrome	17 (54.8)	12 (42.9)	17 (37.0)	14 (37.8)	31 (37.3)	60 (42.3)
Constipation	12 (38.7)	9 (32.1)	18 (39.1)	17 (45.9)	35 (42.2)	56 (39.4)
Decreased appetite	11 (35.5)	9 (32.1)	15 (32.6)	11 (29.7)	26 (31.3)	46 (32.4)
Diarrhoea	11 (35.5)	11 (39.3)	10 (21.7)	9 (24.3)	19 (22.9)	41 (28.9)
Muscle spasms	11 (35.5)	11 (39.3)	14 (30.4)	4 (10.8)	18 (21.7)	40 (28.2)
Lipase increased	6 (19.4)	13 (46.4)	9 (19.6)	9 (24.3)	18 (21.7)	37 (26.1)
Weight decreased	8 (25.8)	8 (28.6)	10 (21.7)	11 (29.7)	21 (25.3)	37 (26.1)
Abdominal pain	5 (16.1)	10 (35.7)	14 (30.4)	5 (13.5)	19 (22.9)	34 (23.9)
Vomiting	6 (19.4)	8 (28.6)	12 (26.1)	8 (21.6)	20 (24.1)	34 (23.9)
Arthralgia	9 (29.0)	7 (25.0)	8 (17.4)	8 (21.6)	16 (19.3)	32 (22.5)
Headache	9 (29.0)	9 (32.1)	9 (19.6)	5 (13.5)	14 (16.9)	32 (22.5)
Dry skin	6 (19.4)	6 (21.4)	13 (28.3)	4 (10.8)	17 (20.5)	29 (20.4)
Back distress	6 (19.4)	5 (17.9)	9 (19.6)	8 (21.6)	17 (20.5)	28 (19.7)
Hypertension	8 (25.8)	6 (21.4)	8 (17.4)	6 (16.2)	14 (16.9)	28 (19.7)
Dyspnea	8 (25.8)	3 (10.7)	10 (21.7)	6 (16.2)	16 (19.3)	27 (19.0)
Anemia	7 (22.6)	5 (17.9)	10 (21.7)	4 (10.8)	14 (16.9)	26 (18.3)
Cough	3 (9.7)	8 (28.6)	8 (17.4)	5 (13.5)	13 (15.7)	24 (16.9)
Dizziness	5 (16.1)	5 (17.9)	8 (17.4)	5 (13.5)	13 (15.7)	23 (16.2)
Rash	5 (16.1)	8 (28.6)	7 (15.2)	3 (8.1)	10 (12.0)	23 (16.2)
Hypokalaemia	6 (19.4)	7 (25.0)	5 (10.9)	2 (5.4)	7 (8.4)	20 (14.1)
Hypophosphataemia	7 (22.6)	3 (10.7)	5 (10.9)	5 (13.5)	10 (12.0)	20 (14.1)
Actinic keratosis	4 (12.9)	4 (14.3)	7 (15.2)	4 (10.8)	11 (13.3)	19 (13.4)
Blood bilirubin increased	5 (16.1)	4 (14.3)	5 (10.9)	4 (10.8)	9 (10.8)	18 (12.7)
Pain in extremity	4 (12.9)	6 (21.4)	3 (6.5)	5 (13.5)	8 (9.6)	18 (12.7)
Pruritus	1 (3.2)	4 (14.3)	7 (15.2)	6 (16.2)	13 (15.7)	18 (12.7)
Maculo-papular rash	3 (9.7)	2 (7.1)	9 (19.6)	4 (10.8)	13 (15.7)	18 (12.7)
Seborrheic keratosis	3 (9.7)	6 (21.4)	6 (13.0)	2 (5.4)	8 (9.6)	17 (12.0)
Insomnia	2 (6.5)	5 (17.9)	3 (6.5)	6 (16.2)	9 (10.8)	16 (11.3)

Preferred term	Second-line (N=31) n (%)	Third-line (N=28) n (%)	Fourth-line (N = 46) n (%)	> Fourth-line (N = 37) n (%)	≥ Fourth-line (N = 83) n (%)	Total GIST patients (N = 142) n (%)
Papilloma skin	1 (3.2)	8 (28.6)	4 (8.7)	2 (5.4)	6 (7.2)	15 (10.6)
Urinary tract infection	3 (9.7)	5 (17.9)	4 (8.7)	3 (8.1)	7 (8.4)	15 (10.6)

1.3.2.1.2. Death

As of August 10, 2019, a total of 256 patients were enrolled into study DCC-2618-01-001, and 42 of them died. Twenty-four of 42 deaths were related to progressive disease, 4 deaths related to GIST, 5 deaths related to AE (2 related to cardiac arrest, each 1 related to myocardial infraction, respiration failure and septicemi), and 9 deaths related to unknown reason.

1.3.2.1.3. Adverse events of special interest

Adverse events of special interest (AESI) include squamous cell carcinoma of skin (SCC), actinic keratosis and keratoacanthoma. As of August 10, 2019, a total of 15 cases (5.9%) of SCC, 32 cases (12.5%) of actinic keratosis and 7 cases (2.7%) of keratoacanthoma were reported. Except for 2 cases (0.8%) of grade 3 SCC, the remaining cases were grade 1 or 2. It is unknown whether these events are related to DCC-2618 (ripretinib, ZL-2307), so they are classified as adverse events of special interest. In the early stage of phase 1 study DCC-2618-01-001, patients didn't receive baseline assessment based on dermatologic examination and may have confounding factors resulting in these events. At present, all patients in study of DCC-2618 (ripretinib, ZL-2307) received baseline assessment based on dermatologic examination and will receive the planned dermatologic examination in the study.

1.3.2.2. Clinical Pharmacokinetics and Pharmacodynamics Markers

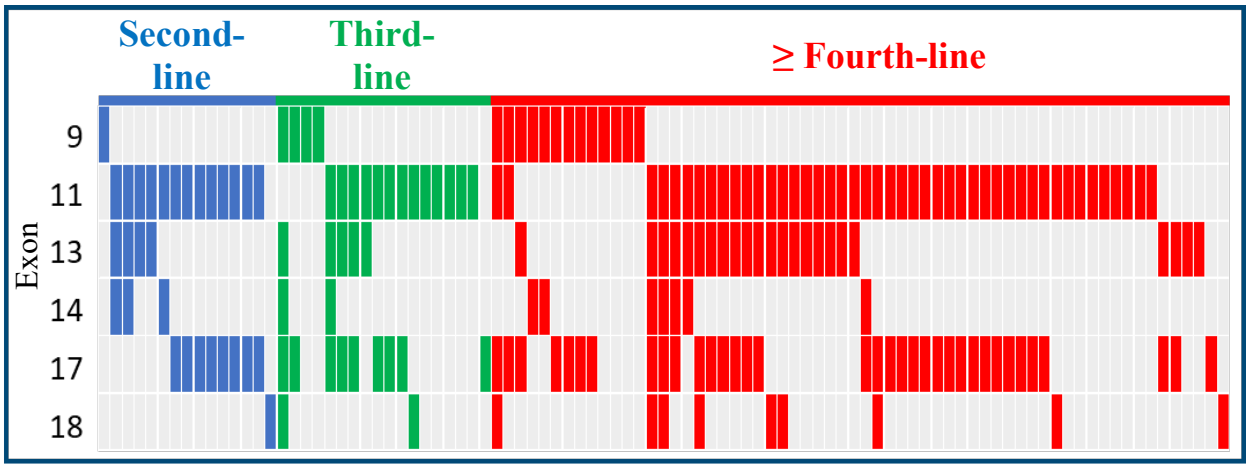
In the non-clinical study, it has been confirmed that DP-5439 is an active metabolite of DCC-2618 (ripretinib, ZL-2307) and its activity features are similar to DCC-2618.

Plasma $T_{1/2}$ of metabolite is longer (30 - 60 hours), indicating QD dosing schedule is feasible. Sub-study of food influence revealed that DCC-2618 (ripretinib, ZL-2307) taken with diet didn't have negative influence on absorption. Please refer to Section 1.5.2 for more information of basis of current study dose, dosing schedule and treatment duration.

In GIST paitents who have previously received multiple therapies, DCC-2618 (ripretinib, ZL-2307) could rapidly eliminate extensive KIT mutation in plasma DNA. In general, on Day 15 of Cycle 1, total plasma concentration (C_{max}) at the start dose of 100 mg BID was very high, more than 5 am (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 inhibiting DCC-2618 (Ripretinib, ZL-2307).

In the phase 1 study, next-generation plasma cell-free DNA (cfDNA) sequencing was carried out in GIST patients at baseline, Week 2, during patients' participation in the study and at the end of study (Figure 3). Mutations were tested and quantified with Guardant 360 v2.9 or v2.10. According to preliminary data (cut-off 18 April 2018), circulation tumor DNA (ctDNA) was tested in most baseline cfDNA. In 131 GIST patients with KIT mutation, KIT mutation was detected in baseline ctDNA test of 95 patients and the mutation range covered exons 9, 11, 13, 14, 17 and 18 (Figure 3). Of 9 enrolled patients with PDGFRA exon 18 mutation, PDGFRA exon 18 mutation was only detected in ctDNA samples of 2 patients (if archived tissues are available, it will be confirmed by testing the tissues).

Figure 3: KIT mutation in baseline ctDNA of 131 GIST patients listed according to treatment line (n = 95)



Each list represents one GIST patient. Each color bar in each line represents one or multiple mutations detected in KIT exons 9, 11, 13, 14, 17 and 18. In patients with KIT exon 9/11 mutations detected in baseline ctDNA, secondary mutation occurred in KIT exons 13, 14, 17 and 18 of second- to ≥ fourth-line patients

1.3.2.3. Clinical Effectiveness

Because phase 1 study DCC-2618-01-001 is ongoing, only source of some clinical data may not be validated or proved. Therefore, there may be changes. The data represent the latest formal cut-off data of the study.

As of March 1, 2019, of advanced GIST patients receiving 150 mg QD RP2D treatment in the phase 1 study, efficacy of 142 patients could be evaluated. ORR of GIST patients receiving 150 mg QD treatment was further analyzed according to treatment line and ORR of GIST patients receiving second-line treatment with DCC-2618 (ripretinib, ZL-2307) was 19.4%.

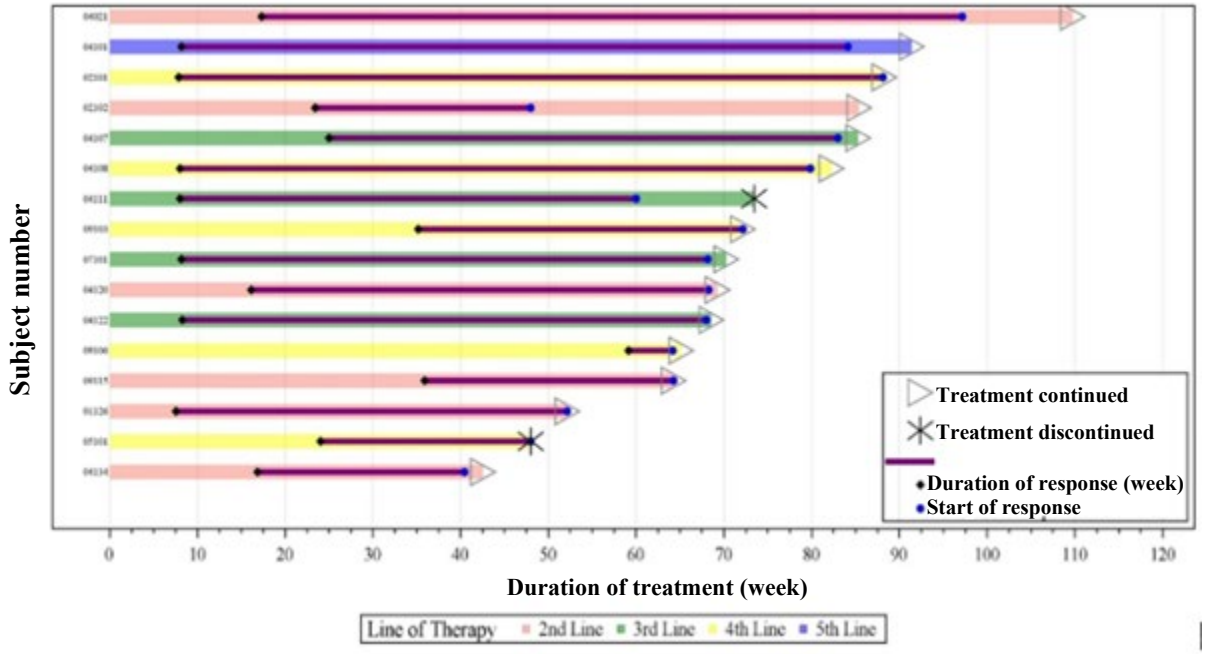
Of GIST patients receiving 150 mg QD treatment (n = 142), the median duration of response of 5 patients (11 patients were censored) was 80 weeks. Duration of response of GIST patients was further summarized according to treatment line. Of patients who received 150 mg QD for second-line treatment, the median response duration was 80 weeks. Figure 4 The duration of response of GIST patients who received 150 mg QD treatment in the preliminary stage of the

escalation and extension period was summarized according to treatment line.

For GIST patients who received 150 mg QD treatment (n = 142), mPFS was 24.1 weeks. The mPFS of patients who received second-line treatment was 41.7 weeks.

Figure 5 is Kaplan-Meier diagram of PFS of GIST patients who received 150 mg QD treatment in the escalation and extension period summarized according to treatment line.

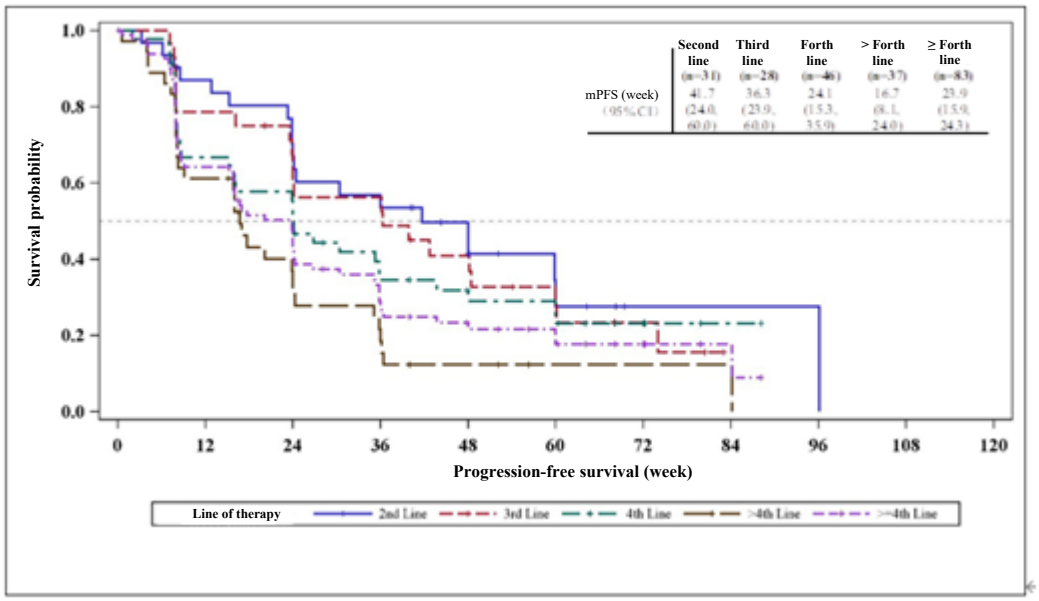
Figure 4: Swimlane diagram of duration of response in GIST patients who received the designated starting dose of 150 mg QD in the escalation and extension period (intent-to-treat population) summarized according to treatment line



Duration of response is defined as period from the first complete response or partial response to progressive disease or death from any cause.

Data cutoff date: March 1, 2019

Figure 5: Kaplan-Meier diagram of PFS of GIST patients who received a starting dose of 150 mg QD in the escalation and extension period summarized according to treatment line (intent-to-treat population)



Data cutoff date: March 1, 2019

1.4. Sunitinib Overview

Sunitinib (Sutent) is a small molecule that can inhibit multiple receptor tyrosine kinase (RTK), some of which are related to tumor growth, pathological angiogenesis and metastatic progression of cancer. Inhibotory effect of sunitinib to many kinases (> 80 kinases) has been evaluated and the substance is confirmed as an inhibitor of platelet-derived growth factor receptor (PDGFRα and PDGFRβ), vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT), FMS tyrosine kinase-3 (FLT3), colony stimulating factor 1 receptor (CSF-1R) and neural glial cell line-derived neurotrophic factor receptor (RET). Inhibitory effect of sunitinib on these RTKs has been proved in biochemical and cell tests and it has been proved that it inhibited the function in cell proliferation assay. In biochemical and cell tests, the main metabolite of sunitinib had similar potency to sunitinib.

In tumor xenograft expressing target RTK, sunitinib can inhibit phosphorylation of many RTKs (PDGFRβ, VEGFR2 and KIT) in vivo and it was proved in some cancer test models that the drug had an inhibitory effect on tumor growth or tumor regression and/or metastasis. Sunitinib had an inhibitory effect on growth of tumor cells expressing maladjusted target RTK (PDGFR, RET or KIT) in vitro and could inhibit tumor angiogenesis dependent on PDGFRβ and VEGFR2 in vivo.

Study NCT#00075218 is a two-arm, international, randomized, double-blinded, placebo-controlled trial and Sutent was used in GIST patients who have progressed during prior imatinib mesylate (imatinib) treatment or are intolerant to imatinib. The study aimed to

compare time to tumor progression (TTP) between patients who received Sutent treatment + best supportive care and those who received placebo + best supportive care. Other objectives included PFS, ORR and overall survival (OS). Patients were randomized (2:1) to receive 50 mg Sutent or oral placebo QD on a 4/2 regimen basis until progressive disease or withdrawal of the study for other reasons. Treatment was unblinded during progressive disease. After that, patients randomized to the placebo group received open Sutent cross treatment while patients randomized to Sutent group could continue the treatment at the investigator's discretion. In the double-blinded treatment period, the median TTP of the Sutent group was 27.3 weeks and that of the placebo group was 6.4 weeks. The median PFS of the Sutent group was 24.1 weeks and that of the placebo group was 6.0 weeks.

1.5. Basic principles

1.5.1. Study Principle

GIST is mainly induced by activated mutation in KIT (about 80%) or relevant PDGFRA (about 10%) receptor tyrosine kinase[11,300]. In GIST patients, exon 9 or 11 mutations are the most common in KIT mutation. Imatinib, as a first-line therapy, generally cannot cure unresectable and/or metastatic diseases and CR rate was about 5% and ORR was 68% [16]. More than 80% GIST patients can benefit clinically from imatinib monotherapy, but could not avoid imatinib drug resistance. More than half of the patients experienced disease progression within 2 years [17]. The main cause for progression was secondary KIT kinase mutation, inducing resistance to imatinib [11]. Although imatinib can effectively inhibit exon 11 mutation in KIT and dose increase to 800 mg was effective to exon 9 mutation, imatinib doesn't or almost doesn't have inhibitory effect on KIT and PDGFRA mutation, especially on mutations of conformation dynamic mediating switch activation [17, 18].

In 2006, sunitinib was approved in America as second-line therapy in GIST patients who have progressed after imatinib treatment or are intolerant to imatinib. Sunitinib has a stronger inhibitory effect on exon 9 mutation than imatinib and a weaker inhibitory effect on exon 11 mutation [14, 17]. In addition, sunitinib has an inhibitory effect on secondary KIT exons 13 and 14 mutations, but only half of patients benefited from it. The median PFS was only 5.5 months [17]. Sunitinib was ineffective in patients with secondary KIT exons 17/18 mutations and PDGFRA exon 18 mutation in activation loop.

DCC-2618 (ripretinib, ZL-2307) is a kinase inhibitor of KIT and PDGFRA and administered orally. DCC-2618 (ripretinib, ZL-2307) 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 switch pocket, and primary and secondary exons 17 and 18 mutations in activation loop conformation-control switch region, primary exon 18 D842V mutation in the PDGFRA conformation-control switch region, and primary mutation of exon 14 in the PDGFRA switch pocket region. DCC-2618 (ripretinib, ZL-2307) can also inhibit mutation-free (original) wild type KIT. DCC-2618 (Ripretinib, ZL-

2307), as an enhanced type II kinase inhibitor, penetrates embedded KIT/PDGFRA switch pocket by binding to extensively inhibit the wild type (original) and mutation of KIT/PDGFRA. DCC-2618 (ripretinib, ZL-2307) is expected to provide benefits for all patients with primary mutations, including patients who didn't respond to inhibition of imatinib and had extensive drug-resistant mutations. When there is no KIT/PDGFRA mutation (WT GIST), it is known that activation of KIT protein in GIST is very strong. In imatinib-resistant GIST, KIT expression is always high[27, 28]. These findings reveal that KIT plays an important role in the pathogenesis of GIST.

In phase 1 study DCC-2618-01-001, DCC-2618 (ripretinib, ZL-2307) showed a satisfactory preliminary clinical activity in advanced GIST patients. In patients receiving a treatment dose ≥ 100 mg QD, 3-month DCR of second-, third- and ≥ fourth-line patients was 79% (N = 25), 82% (N = 29) and 64% (N = 91), respectively. ORR of second- and third-line GIST patients was 24% and that of ≥ fourth-line patients was 9%. In phase 1 study[29], KIT drug-resistant mutation was observed in second-, third- and fourth-line patients, including exons 13, 14, 17 and 18 or combined mutation, which supported the need of covering extensive mutations in imatinib later treatment lines.

In the ongoing phase 1 study, DCC-2618 (ripretinib, ZL-2307) covered an extensive rane of KIT and PDGFRA mutants, involving KIT exons 9, 11, 13, 14, 17 and 18, PDGFRA exons 12, 14 and 18, wild type KIT and PDGFRA. Meanwhile, drug toxicity was controllable and efficacy data were ideal. Therefore, Deciphera initiated a phase 3 study (INTRIGUE) in GIST patients who have previously received imatinib treatment to evaluate the efficacy of DCC-2618 (ripretinib, ZL-2307). This is a two-arm, randomized, open-label, international, multicenter study to compare the efficacy of DCC-2618 (ripretinib, ZL-2307) and sunitinib in GIST patients who have progressed after prior imatinib treatment or are intolerant to imatinib.

Zai Lab will carry out phase 2 bridging study of the study. A study design similar to study INTRIGUE will be adopted and study population is also consistent with study INTRIGUE, that is, patients with advanced GIST who have progressed after prior imatinib treatment or are intolerant to imatinib. The GIST epidemiology, pathogenesis and clinical treatment practice in Chinese and western medicine are highly similar. If study data of DCC-2618 and INTRIGUE are consistent in Chinese GIST patients receiving the same line of treatment, it will support that DCC-2618 is used in the indication in China.

1.5.2. Rationale for Dose, Regimen and Treatment Duration

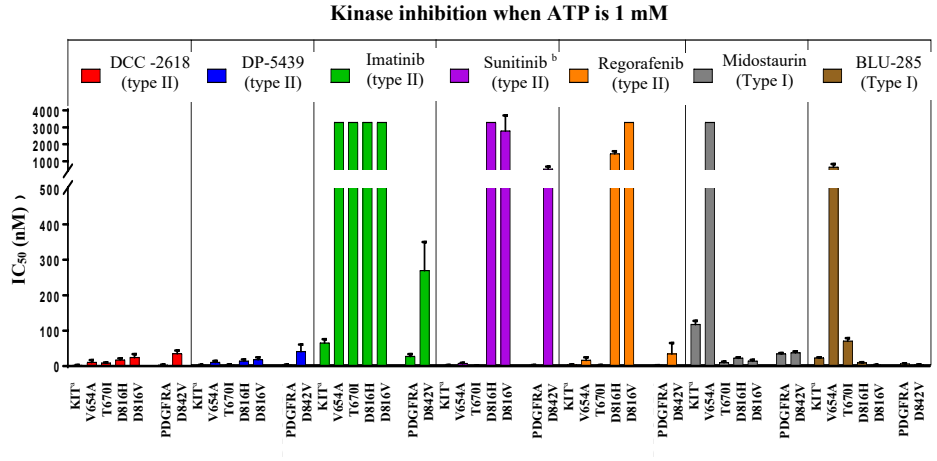
1.5.2.1. Non-clinical pharmacological and clinical pharmacokinetic analysis of supporting the best phase 3 dose selection

This section describes the scientific basis for selecting the dosing regimen of 150 mg QD of DCC-2618 (Ripretinib, ZL-2307) for advanced GIST patients in the phase 3 study. Dose suggestion is based on non-clinical pharmacology, clinical PK evaluation and PD results of ongoing phase 1 study (as of April 18, 2018).

1.5.2.1.1. In Vitro Pharmacology

In vitro pharmacological study proved that DCC-2618 (Ripretinib, ZL-2307) and its metabolite DP-5439 can potently inhibit wild-type, carcinogenic KIT and PDGFRA mutants, and IC_{50} was 3-36 nM (Figure 6). The section provides the available data of KIT inhibitors including imatinib, sunitinib, midostaurin, regorafenib and BLU-285 for reference. At relevant ATP cell levels (1 nM), DCC-2618 (ripretinib, ZL-2307) extensively inhibits KIT exons 11, 13, 14 and 17 mutants and PDGFRA exon 18 mutant. Other type II inhibitors don't have blocking effect on exon 17 mutants such as D816V KIT, while type I inhibitors have a weaker inhibitory effect on exon 13/14 mutants.

Figure 6: Inhibition of DCC-2618 (ripretinib, ZL-2307) to PDGFRA and KIT mutation



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

Imatinib, sunitinib, regorafenib and DCC-2618 (Ripretinib, ZL-2307) generated active metabolites. The following doses are mainly based on pharmacological characteristics of drug prototype compound. Unbound fraction (fu) of imatinib and sunitinib was reported to be the same (5%), but in vitro effect of sunitinib was 6 times (WT KIT) that of imatinib. For the treatment of GIST, the corresponding 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). Regorafenib can inhibit several exon 17 mutants (not indicated by data) and has a stronger activity. Therefore, a reduced dose also has a therapeutic effect.

In vitro fu of DCC-2618 (Ripretinib, ZL-2307) 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 (Ripretinib, ZL-2307) (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 (Ripretinib, ZL-2307) (294 µmol, 150 mg) was close to that of regorafenib (331 µmol, 160 mg). However, because inhibitory effect of DCC-2618

(Ripretinib, ZL-2307) was stronger on KIT mutant exons 17 and 11, its optimal dose may be lower.

1.5.2.1.2. In Vivo Pharmacology

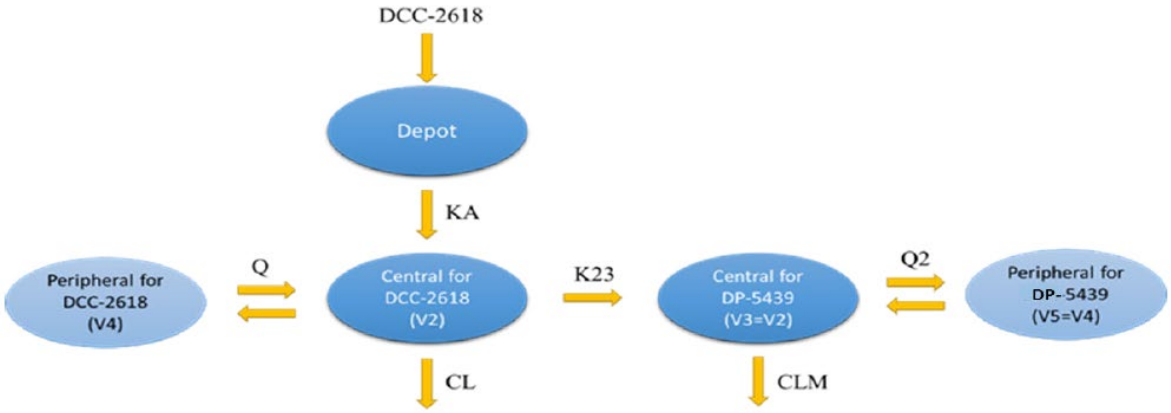
In exon 11 mutant KIT GIST T1 cell line xenograft mouse model, within 8 hours after single oral dose of DCC-2618 (Ripretinib, ZL-2307) at 50 mg/kg, inhibition rate of KIT signal transduction reached 69-88%; within 12 hours after administration, the inhibition rate remained 40%. After orgal administration to the GIST T1 xenograft model, 50 mg/kg DCC-2618 (Ripretinib, ZL-2307) could significantly inhibit tumor growth, with an inhibition rate reaching 90%. In imatinib-resistant GIST patient-derived xenograft model, 100 mg/kg QD or 50 mg/kg BID DCC-2618 (Ripretinib, ZL-2307) could completely stop tumor growth. In Kasumi-1 AML xenograft model expressing primary exon 17 KIT mutation (N822K KIT), DCC-2618 (Ripretinib, ZL-2307) 100 mg/kg and 50 mg/kg showed powerful efficacy, while imatinib 50 mg/kg BID was ineffective. In HMC1.2 mastocytosis xenograft model carrying exon 11 V560D and exon 17 D816V double mutation, after oral administration of DCC-2618 (ripretinib, ZL-2307) at 25 and 100 mg/kg/day, dose-related tumor burden decrease was observed. In H1703 lung cancer xenograft model with PDGFRA amplification, when the drug was administered at 25 mg/kg/day, tumor growth was almost inhibited. When the drug was administered at 100 mg/kg/day, tumor regression was observed.

According to in vivo pharmacological study, under the steady state, in terms of $AUC_{0\text{-}24hr}$ of DCC-2618 (Ripretinib, ZL-2307) and DP-5439, it was confirmed that target PK exposure for suppressing tumor growth was 10,000 ng·h/mL.

1.5.2.1.3. Clinical Drug Pharmacokinetic Assessment

Combined BID and QD data were collected from patients with advanced malignant tumors in the ongoing phase 1 study of DCC-2618 (ripretinib, ZL-2307) for population PK analysis (study protocol DCC-2618-01-001). Please see Figure 7 for model structure. Two-chamber model was used to describe PK characteristics of DCC-2618 (ripretinib, ZL-2307) and DP-5439. Reservoir means GI of oral DCC-2618 (ripretinib, ZL-2307). KA is first-order absorption rate constant of DCC-2618 (Ripretinib, ZL-2307); K23 is the first-order rate constant of DCC-2618 (Ripretinib, ZL-2307) metabolizing its active metabolite DP-5439 through CYP3A4/5. CL and CLM represent DCC-2618 (Ripretinib, ZL-2307) 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 (Ripretinib, ZL-2307) to avoid over-parametrization.

Figure 7: 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 n = 44) showed PK of DCC-2618 (Ripretinib, ZL-2307) and DP-5439 in cancer patients was dose proportionally. See Table 4 for steady-state PK exposure predicted by the model.

Table 4: Typical steady-state drug toxicokinetics exposure in patients with advanced malignant tumor predicted by models of DCC-2618 (ripretinib, ZL-23070 and DP-5439

Dose interval	Dose	Analyte	C_{trough} (ng/mL)	C_{max} (ng/mL)	$AUC_{0\text{-}24hr}$ (ng·h/mL)
BID	20	DCC-2618	131	171	3736
		DP-5439	207	225	5211
		Combination	338	396	8947
	30	DCC-2618	197	257	5603
		DP-5439	310	337	7816
		Combination	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

Dose interval	Dose	Analyte	C_{trough} (ng/mL)	C_{max} (ng/mL)	AUC_{0-24hr} (ng·h/mL)
		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_{0-24hr} = 0-24 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 (Ripretinib, ZL-2307) to typical cancer patients, combining stable PK exposure (AUC_{0-24hr}) of DCC-2618 (Ripretinib, ZL-2307) and DP-5439 was more than 10,000 ng·h/mL efficacy threshold confirmed by xenograft mice institution. However, PK of DCC-2618 (ripretinib, ZL-2307) and DP-5439 varied greatly among patients.

One hundred studies were simulated with group PK model and each study contained 100 subjects; 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 re-simulated with 100 mg QD, it was estimated that 87.9% of patients would reach the efficacy threshold.

1.5.2.1.4. Conclusion

It is recommended oral DCC-2618 (Ripretinib, ZL-2307) 150 mg QD be taken as the optimal dose regimen for the treatment of GIST for the following reasons:

- Comparison of in vitro pharmacological properties between DCC-2618 (Ripretinib, ZL-2307) and three approved target therapeutic drugs for the treatment of GIST showed that when treating GIST patients, effectively daily dose of DCC-2618 (Ripretinib, ZL-2307) was ≤ 160 mg.
- In vivo pharmacological study in xenograft mouse model indicated that target combination PK exposure (AUC_{0-24hr} = 10,000 ng·h/mL) of DCC-2618 (Ripretinib, ZL-2307) and DP-5439 could inhibit tumor growth. For 93.6% of patients, it is estimated that PK value can be maintained above the threshold by taking 150 mg of the study drug daily.
- According to in vitro and in vivo pharmacological data, 150 mg QD predication 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 the BID regimen by which the target exposure can be realized to meet efficacy requirement, daily administration regimen is more convenient and may improve treatment compliance. Therefore, 150 mg QD is better than the similar daily dose BID.
- Because PK varies greatly between individuals, when the administration dose is lower than 150 mg, the lower the dose, the more the patients with a PK exposure lower than the efficacy threshold. On the other hand, a higher administration dose is unlikely to further improve the efficacy.
- For most patients (87.9%), it is estimated that a dose of 100 mg QD can reach the effective exposure target. If individual patient is unable to tolerate 150 mg QD, the dose can be reduced to 100 mg QD without influencing the efficacy.
- PK-efficacy and PK-safety evaluation are ongoing to confirm the selection of 150 mg QD as the best treatment regimen of DCC-2618 (ripretinib, ZL-2307) for GIST patients.

2. Study Objectives

2.1. Primary objective

- To assess the efficacy (progression-free survival [PFS], by independent radiologic review) of DCC-2618 (ripretinib, ZL-2307) and sunitinib in patients with advanced gastrointestinal stromal tumors after treatment with imatinib.

2.2. Secondary objective

- To assess objective response rate (ORR) by independent radiologic review using RECIST v1.1-GIST-specific criteria
- To assess disease control rate (DCR) by independent radiologic review
- To assess PFS based on Investigator assessment
- To assess overall survival (OS)
- To compare the safety profile of DCC-2618 (ripretinib, ZL-2307) to the safety profile of sunitinib
- To assess pharmacokinetic characteristics of DCC-2618 (ripretinib, ZL-2307)

2.3. Exploratory objectives

- To evaluate potential biomarkers in blood or tumor tissue which might predict response to DCC-2618 (ripretinib, ZL-2307)
    - To understand potential drug resistance mechanism to DCC-2618 (ripretinib, ZL-2307) in GIST.
    - To characterize KIT and PDGFRA mutations at baseline and DCC-2618 (ripretinib, ZL-2307)-driven longitudinal mutant allele frequency changes in plasma.

Note: Blood samples and tumor tissues for exploratory purpose will be collected after obtaining the approval of China Human Genetic Resources Administration Office.

3. Study Design

3.1. Overview of Study Design

This is a randomized, open-label, multicenter phase 2 clinical study to compare the efficacy and safety of DCC-2618 (ripretinib, ZL-2307) to sunitinib in GIST patients who progressed on or were intolerant to first-line anticancer treatment with imatinib.

Approximately 98 patients will be randomized in a 1:1 ratio to DCC-2618 (ripretinib, ZL-2307) 150 mg QD by continuous administration or sunitinib 50 mg QD, 4 weeks on, 2 weeks off. Up to 10% of randomized patients may have KIT/PDGFRA WT GIST (wild-type KIT and wild-type PDGFRA regardless of the mutational status of any other gene).

Randomization will be stratified by:

• KIT exon 11 mutation; KIT exon 9 mutation; other (KIT/PDGFRA WT or other KIT [lacking exon 9 or 11]/PDGFRA mutation);

The primary endpoint of the study will be evaluated using the modified Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1-GIST-specific based on independent radiologic review.

Upon disease progression by RECIST-GIST-specific based on independent radiologic review, patients will discontinue their assigned treatment.

If the investigator doesn't hope to confirm by the independent radiologic review or hopes to terminate the patient's treatment according to progressive disease based on "RECIST v1.1-GIST-specific Criteria" before obtaining results of the independent radiologic review, it is necessary to discuss with the sponsor.

3.2. Number of patients

Approximately 98 patients will be randomized in a 1:1 ratio to receive DCC-2618 (ripretinib, ZL-2307) 150 mg QD by continuous administration or sunitinib 50 mg QD, 4 weeks on, 2 weeks off.

3.3. Study duration

Patients will receive treatment until progressive disease confirmed by the independent radiologic review based on "RECIST v1.1-GIST-specific Criteria", intolerable toxicity or withdrawal of consent.

Patients will discontinue the study drug treatment if patients have progressive disease based on

assessment of the independent radiologic review using “RECIST v1.1-GIST-specific Criteria”.

The longest medication duration of patients is 2 years. For patients with evidence of clinical benefit from the drug and tolerance to the drug and following the study procedure, the treatment duration will be prolonged by reaching an agreement between the sponsor and the investigator.

The study will be terminated when the last patient has progressive disease or 20 months after finishing enrollment or when the sponsor determines to terminate the study, whichever occurs first.

4. Study population

4.1. Inclusion criteria

Eligible patients must meet all the following criteria in order to be included in this clinical trial:

1. Male or female patients ≥18 years of age.
2. Histological diagnosis of advanced GIST and capability of providing tumor tissue sample (the interval between tumor tissue collection and signing of informed consent form should be less than 3 years). Otherwise, biopsy is required.
3. Provide molecular test report with KIT/PDGFRA mutation status prior to randomization. Mutation status must be identified by tissue-based PCR or sequencing analysis. If molecular test report is unusable or insufficient, an archived tumor tissue sample or fresh live tissue should be tested to confirm mutation status prior to randomization.
4. Patients must have progressed on imatinib or have documented intolerance to imatinib. Subjects must have discontinued imatinib treatment 10 days prior to the first dose of the study drug. All prior imatinib treatments will be considered as first-line (such as imatinib adjuvant therapy and imatinib dose increase).
5. ECOG PS of 0-2.
6. Female patients of childbearing potential must have a negative serum beta-human chorionic gonadotropin (β-hCG) pregnancy test at screening.
7. Subjects of reproductive potential should adopt effective contraceptive measures.
8. At least 1 measurable lesion according to the “RECIST v1.1-GIST-specific Criteria" (non-nodal lesions must be ≥1.0 cm in the long axis or ≥ double the slide thickness in the long axis); obtaining radiographic image results within 28 days prior to the first dose of study drug.
9. Good organ function and bone marrow reserve function, including:
    - Neutrophil count (ANC) ≥ 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
- Creatinine clearance ≥ 50 mL/min (based on Cockcroft-Gault Formulas for calculation)

  Note: Patients should receive no corrective treatment with granular colony stimulating factor or interleukin-11, infusion of red blood cells or platelets or other blood products within 2 weeks prior to detecting haematology.
- Prothrombin time (PT), 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 study 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 study drug, excluding alopecia and ≤ Grade 3 clinically asymptomatic lipase, amylase, and creatine phosphokinase laboratory abnormalities.
11. Patient is capable of understanding and complying with the protocol. Subjects should sign the written informed consent before any study-related procedures were performed.

4.2. Exclusion criteria

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

1. Treatment with any other line of therapy in addition to imatinib for advanced GIST. Imatinib-containing combination therapy in the first-line treatment should not be enrolled.
2. Patients with a prior or concurrent malignancy whose natural history or treatment have the potential to interfere with the safety or efficacy assessment of this clinical trial are not eligible. For example, patients who received adjuvant treatment for cancer and used drugs which have potential activity to GIST or are prohibited by study protocol are not eligible.
3. Patient has known active central nervous system metastases.
4. New York Heart Association class II - IV heart disease, myocardial infarct, active ischemia or any other uncontrolled cardiac condition within the first 6 months of the first dose of study drug such as angina pectoris, clinically significant cardiac arrhythmia requiring therapy, uncontrolled hypertension or congestive heart failure.
5. Left ventricular ejection fraction (LVEF) < 50%.
6. Arterial thrombotic or embolic events such as cerebrovascular accident (including ischemic attacks) or hemoptysis within the first 6 months of the first dose of study drug.

7. Venous thrombotic events (e.g. deep vein thrombosis) or pulmonary arterial events (e.g. pulmonary embolism) within 1 month before the first dose of study drug. Patients on stable anticoagulation therapy for at least one month are eligible.
8. 12-lead ECG demonstrating QT interval (QTc) corrected by Fridericia's formula >450 ms in males or > 470 ms in females at screening or history of long QT interval syndrome.
9. Use of moderate or strong inhibitors and/or inducers of cytochrome P450 (CYP) 3A4 within 14 days or 5 x the half-life (whichever is longer) prior to the first dose of study drug, including certain herbal medications (eg, St. John's Wort) and consumption of grapefruit or grapefruit juice within 14 days prior to the first dose of study drug. For CYP3A4 enzyme inhibition/induction-related drugs, please refer to the website of the Indiana University, School of Medicine (http://medicine.iupui.edu/clinpharm/ddis/main- table/).
10. Use of known substrates or inhibitors of breast cancer resistance protein (BCRP) transporters within 14 days or 5 x the half-life (whichever is longer) prior to the first dose of study drug. For information of inhibitors and substrates, please refer to Food and Drug Administration (FDA) website: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm.
11. Major surgeries (e.g. Abdominal laparotomy) within 4 weeks of the first dose of study drug; all major surgical wounds must be healed and free of infection or dehiscence before the first dose of study drug.
12. Any other clinically significant comorbidities, such as uncontrolled pulmonary disease, active infection, or any other condition, which in the judgment of the investigator, could compromise compliance with the protocol, interfere with interpretation of the study results, or predispose the patient to safety risks.
13. Known human immunodeficiency virus or hepatitis C infection only if the patient is taking medications that are excluded per protocol, hepatitis B virus (HBV) DNA > 2000 IU/ml or > 10^4 copies/ml.
14. Female patients who are pregnant or lactating or who plan to become pregnant during the study treatment period.
15. Known hypersensitivity to any component of the study drug. Patients with Stevenson Johnson syndrome in previous TKI treatment need to be excluded.
16. Gastrointestinal abnormalities including but not limited to:
    - inability to take oral medication
    - malabsorption syndrome
    - Requiring intravenous (IV) nutrition

17. Any active hemorrhages, excluding hemorrhoids or gum bleeding.

5. Administration and Management of Study drugs

5.1. Sunitinib

5.1.1. Sunitinib Description

Sunitinib will be provided as scored hard capsules and contain sunitinib malate equivalent to 12.5 mg of sunitinib. In active ingredients include mannitol, croscarmellose sodium, povidone (K-25) and magnesium stearate.

5.2. DCC-2618 (Ripretinib, ZL-2307)

5.2.1. Description of DCC-2618 (ripretinib, ZL-2307)

DCC-2618 (ripretinib, ZL-2307) is a 50 mg oral tablet. The tablet contain active ingredient. Its formulation is amorphous dispersion and cellulose acetate succinate (mass ratio of grade H polymer matrix [33.33%] is 25% [w/w]). Other excipients include microcrystalline cellulose (Avicel PH-101) (29.84%), lactose 310 (29.83%), crosslinked polyvinylpyrrolidone (5%), fumed silica (CabOSil M5P or Syloid 244FP) (1%) and magnesium stearate (1%).

5.3. Dosage and route of administration of study drugs

The study drug can be distributed only under the supervision of the investigator or authorized designated personnel and administered to subjects of the study only. Patients will be randomized to receive DCC-2618 (ripretinib, ZL-2307) 150 mg QD by continuous administration based on a 42-day cycle, or sunitinib 50 mg QD in 6 weeks (42 days) with 4 weeks continuous dosing followed by 2 weeks break. According to the approved package insert, dose adjustment of sunitinib is allowed.

The investigator or designated personnel must guide patients to take DCC-2618 (ripretinib, ZL-2307) according to the following method:

- It should be taken at the same time each day.
- Patient should take study srug with or without food.
- Swallow as a whole. Tablets must not be crushed, chewed or dissolved in liquid or food.
- Administration date, dose and time of DCC-2618 (ripretinib, ZL-2307) should be recorded 3 days before and on the day of PK sampling.

If the patient forgets to take DCC-2618 (ripretinib, ZL-2307) at the predetermined time, the patient can take the predetermined dose within 8 hours upon the predetermined time. If it has been over 8 hours from the predetermined time, the missing dose must be ignored and the next predetermined dose of drug can be taken to continue the treatment.

Please refer to the approved package insert for description of administration of sunitinib.

On the scheduled study visit date, patients will be informed of taking the study drug at study site according to Table 1 (Schedule of Assessments). Administration of the study drug must be carried out at study site after finishing pre-dose assessment. Administration date, dose and time of the study drug must be recorded in source documents of patients.

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

Please refer to Section 7.12 and the approved package insert of sunitinib for information of overdose.

5.4. Dose interruption and adjustment of study drugs

Dose interruption and adjustment of sunitinib will be carried out according to guidelines in the approved package insert.

If AE occurs, the investigator can determine interrupt administration of DCC-2618 (ripretinib, ZL-2307) or adjust its dose (that is, dos reduction). If dose adjustment is required for other reasons, it is necessary to discuss with the sponsor and make a decision. Interruption duration should not be more than 28 consecutive days.

For sunitinib and DCC-2618 (ripretinib, ZL-2307), department visit and assessment should be continued during dose interruption according to Table 1 (Schedule of Assessments). If administration is resumed after dose interruption, the investigator must continue administration according to the source visit schedule from C1D1 (that is, calculate the number of days of cycle continuously and not discontinue calculation due to dose interruption). If dose interruption is more than 28 days, treatment with the study drug will be terminated in this patient. If the regimen used by the patient is 4-week administration followed by 2-week withdrawal, the 28-day time limit also includes the 2-week withdrawal.

5.4.1. Interruption of the study drug due to planned medical procedure

According to the approved package insert, sunitinib should be interrupted if major surgical procedure is required.

For DCC-2618 (ripretinib, ZL-2307), surgery performed in patients during the study, surgical range and postoperative healing speed should be considered. It applies to the following guidelines:

- Scheduled minimally invasive surgery: 3 days before and after the surgery, DCC-2618 (ripretinib, ZL-2307) must be discontinued for 3 days.
- Scheduled major surgery: 5 days before and after the surgery, DCC-2618 (ripretinib, ZL-2307) must be discontinued for 5 days.
- Unscheduled/emergent surgery: DCC-2618 (ripretinib, ZL-2307) must be discontinued immediately and resumed according to requirements of the above minimally invasive and/or major surgery.

5.4.2. Dose interruption and adjustment of DCC-2618 (ripretinib, ZL-2307) caused by adverse events

If AE occurs, the investigator can determine to discontinue DCC-2618 (ripretinib, ZL-2307) or reduce its dose at any time according to guidelines in Table 6, Table 7 Table 8, Table 9 and Table 10. It is necessary to discuss dose reduction with the sponsor in advance as far as possible. If DCC-2618 (ripretinib, ZL-2307) is resumed after interruption, the patient should use the drug according to the former administration schedule.

If any patient needs to use the drug at a dose lower than 50 mg QD, or if dose for the patient has been reduced and progressive disease is confirmed by independent radiologic reviewers, the patient must discontinue the study drug and receive end of treatment (EOT) visit and safety follow-up visit. In addition, OS of the patient must be followed up.

Table 5: Dose reduction steps of DCC-2618 (ripretinib, ZL-2307)

Initial dose of DCC-2618	The 1st dose reduction	The 2nd dose reduction
150 mg QD	100 mg QD	50 mg QD

If AE is recovered to grade 1 or baseline level, the dose should be increased for the patient. It is necessary to increase the dose for the patient to the dose level at AE occurrence. If dose level is reduced to the first dose reduction level and AE is recovered to grade 1 or baseline level, the patient can resume the drug according to the starting dose level. If the patient reduces the dose twice continuously and AE is recovered to grade 1 or baseline level after the second dose reduction, the drug should be administered at the first dose reduction level which should be maintained for at least 1 cycle continuously before increasing the dose to the starting dose level.

If an AE leads to dose adjustment and is not recovered to grade 1 or baseline level within 1 cycle (42 days), DCC-2618 (ripretinib, ZL-2307) must be discontinued, unless the investigator considers the event is not clinically significant. In such case, feasibility of resuming the drug at a dose reduction level should be judged after consulting the sponsor.

Table 6: Principle of dose adjustment of DCC-2618 (ripretinib, ZL-2307) due to skin toxicity (except Alopecia) and joint pain/myalgia

Toxicity Grade*	Dose Adjustment Principle
Grade 1	Adopt supportive treatment of study institution and continue DCC-2618 at the current dose
Grade 2	Adopt supportive treatment of study institution and continue DCC-2618 at the current dose • If the event is not improved within 7 days, DCC-2618 will be discontinued • If the event is recovered to grade 1 or baseline level within 7 days, DCC-2618 will be resumed at the same dose level • If the event is recovered to grade 1 or baseline level after 7 days, DCC-2618 will be resumed at a reduced dose level • If the event recurs, DCC-2618 will be resumed at a reduced dose after the event is

Toxicity Grade*	Dose Adjustment Principle
	recovered to grade 1 or baseline level, regardless of the time to recovery • If the event maintains grade 1 or baseline level for at least 1 administration cycle (42 days) after dose reduction, it can be considered to increase the dose of DCC-2618 by a dose level
Grade 3	Adopt supportive treatment of the study institution • Withhold DCC-2618 for at least 7 days or until the event resolves to grade 1 or baseline level (28 days at most). Resume DCC-2618 at a reduced dose • If the event maintains grade 1 or baseline level for at least 1 administration cycle (42 days) after dose reduction, it can be considered to increase the dose of DCC-2618 by a dose level
Grade 4	Discontinuing DCC -2618.
Grade: any	**Stevens-Johnson syndrome:** If patients have developed Stevens-Johnson syndrome (SJS)/hypersensitivity reaction during treatment period, the DCC-2618 must be discontinued permanently. Patients should be transferred to hospital immediately to receive clinical assessment and supportive care/treatment accordingly. DCC-2618 should not be resumed due to risks of SJS/hypersensitivity reaction recurrence. It is not suggested to use other similar drugs (TKI for GIST) to avoid SJS recurrence because similar reaction occurred during regorafenib treatment in a patient who was diagnosed with SJS during DCC-2618 treatment.
* The severity of AEs outside the CTCAE is confirmed according to Table 12.	

Table 7: Principle of dose adjustment of DCC-2618 (ripretinib, ZL-2307) due to hypertension

Toxicity Grade	Dose Adjustment Principle
Grade 1 **Prehypertension (systolic blood pressure 120-139 mmHg or diastolic blood pressure 80-89 mmHg)**	Monitor BP continuously Continue DCC-2618 administration at the current dose level
Grade 2 **Systolic blood pressure 140 - 159 mmHg or diastolic blood pressure 90 - 99 mmHg or elevation > 20 mmHg (diastolic blood pressure) with accompanying symptoms or blood pressure > 140/90 mmHg (previous normal blood pressure)**	Adopt antihypertensive therapy to make diastolic blood pressure ≤ 90 mmHg or systolic blood pressure ≤ 140 mmHg Continue DCC-2618 administration at the current dose level If a 20 mmHg symptomatic blood pressure increased occurs (diastolic blood pressure), DCC-2618 should be discontinued until symptom resolved and diastolic blood pressure ≤ 90 mmHg DCC-2618 is resumed at the same dose level
Grade 3 **Systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg or more than one hypotensor or more intensive treatment required**	Adopt antihypertensive therapy to make diastolic blood pressure ≤ 90 mmHg or systolic blood pressure ≤140 mmHg • Starting hypotensor treatment and/or • Increase the dose of current hypotensor and/or • Add other hypotensor If symptomatic, DCC-2618 should be discontinued until diastolic blood pressure ≤ 90 mmHg and/or systolic blood pressure ≤ 140 mmHg and symptom resolved DCC-2618 is resumed at the same dose level If BP is uncontrollable after adding new drug or more intensive treatment, DCC-2618 will be reduced by a dose level If grade 3 hypertension occurs after dose reduction of DCC-2618 and antihypertension therapy, DCC-2618 will be reduced by a dose level again
Grade 4 **Life-threatening (such as malignant hypertension, transient or permanent nerve damage or hypertensive crisis)**	Adopt antihypertension therapy according to guidelines for the treatment of hypertension Discontinuing DCC -2618.

BP = Blood pressure

*If BP is controllable within at least 28 days, the investigator may increase the dose of DCC-2618 again according to conditions.

Table 8: DCC-2618 Dose Modifications for Left Ventricular Systolic Dysfunction

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

Table 9 DCC-2618 Dose Modifications for Isolated Bilirubin Increased

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

Table 10: Principle of dose reduction of DCC-2618 (ripretinib, ZL-2307) due to treatment-related adverse events not mentioned above

Toxicity Grade	Dose Adjustment Principle[1]
Any grade 3 or 4 events	Discontinue DCC-2618 until the event is relieved to grade 1 or baseline level. After the event is relieved to grade 1 or baseline level, DCC-2618 should be administered at a lower dose level. If the patient tolerates the reduced dose and the event doesn't occur within at least 28 days, DCC-2618 can be increased to the former dose level again.
Asymptomatic/not clinically significant grades 3 or 4 laboratory abnormality (including CPK and lipase) lasting ≤ 10 days	Monitor clinical symptoms closely and continue administration of DCC-2618 at the current dose level. Carry out laboratory test within 10 days.
Asymptomatic/not clinically significant grades 3 or 4 laboratory indicator abnormal (including CPK and lipase) lasting > 10 days	Monitor clinical symptoms closely; if it is a grade 4 event, discontinue DCC-2618 until the event is recovered to grade 3; after the event is recovered to grade 3, resume DCC-2618 at the current dose level or reduce to a lower dose level by he investigator according to conditions after discussing with the sponsor. For asymptomatic grades 3 or 4 lipase or CPK increase, dose interruption is not required;
Clinically significant grade 3 or 4	Discontinuing DCC-2618 dosing. If the investigator considers

laboratory abnormality (including CPK and lipase)	that resuming DCC-2618 meets the patient's best interest, it is necessary to discuss with the sponsor to confirm whether to resume the drug.

CPK = Creatine phosphokinase

[1] Dose adjustment principle of laboratory abnormality is based on laboratory test results of study institution.

5.5. Packaging and Labeling

DCC-2618 (ripretinib, ZL-2307) will be provided by the sponsor. The drug will be prepared to oral tablets containing 50 mg of the study drug and packaged in high density polyethylene (HDPE) bottles with child-resistant closures.

Sutent® (sunitinib malate) 12.5 mg oral capsules will be supplied in the original package in HDPE medicine bottles and repasted with labels by the sponsor.

5.6. Storage Condition of Study drug

DCC-2618 (ripretinib, ZL-2307) bottles must be sealed up and stored at 5°C - 25°C (41°F-77°F). Protect from high humidity and intensive sunshine (such as places close to shower cubicle in the bathroom). A deviation of 2°C-27°C (35.6°F-80.6°F) is allowed.

Please refer to the package insert for information of storage and disposal of sunitinib.

The study drug must be stored in a safety place with restricted access and temperature monitored at study site.

5.7. Study drug Compliance

To ensure compliance of the study drug, the investigator or designated personnel must monitor all administrations of the study drug by study site. At each visit, personnel of study site must review patients' compliance to the study drug and remind patients to take the study drug as required. Compliance should be assessed by continuously counting the study drug.

If the patient still doesn't comply with administration of the study drug after education, the investigator must contact and discuss with the sponsor to make the patient withdraw from the study.

5.8. Counting of Study drug

The investigator is responsible for counting the study drug at study site. The investigator must ensure administration of the study drug only in compliance with the study protocol. If conditions allow, the investigator can assign the responsibility of counting the study drug to pharmacist or other appropriate personnel. Record of drug counting must be kept by clinical study site and the followings should be described in record: date of the study drug sent to study site, inventory of the study drug at study site, amount of the study drug distributed to each patient, amount of the study drug returned by each patient, amount of the study drug returned

to the sponsor and amount of the study drug destructed at study site Counting record should include date, amount, bottle number and patient number. Study monitor should continuously review drug accountability at study site during visit. The sponsor should be informed of any distribution mistake or deviation immediately.

Patients must be told to return all bottles of unused, partially used and used study drugs to study site at each visit. Throughout the study, study monitor must verify record and inventory of the study drug.

5.9. Disposal, Return or Keep of the Unused Study drugs

Patients must be told to return all bottles of used, partially used and unused study drugs. Personnel of study site or pharmacy personnel (if applicable) must keep all materials returned by patients until they are returned to the sponsor or destructed by study site. If the study drug is destructed at study site, the investigator or designated personnel must ensure to destruct these materials according to applicable environmental protection law and regulations, institutional policies and any special instructions provided by the sponsor. Destruction must be recorded in detail.

5.10. Method for Assigning Subjects into Treatment Groups

Patients will be randomized at 1:1 to DCC-2618 (ripretinib, ZL-2307) 150 mg group or sunitinib 50 mg group. Patients with KIT/PDGFRA WT GIST (KIT and PDGFRA wild-type, regardless of status of any other gene mutations) accounted for at most 10% of all enrolled patients. Stratification factors of randomization include:

- KIT exon 11 mutation; KIT exon 9 mutation; other (KIT/PDGFRA WT or other KIT [lacking exon 9 or 11]/PDGFRA mutation);

5.11. Blinding and Unblinding

This is an open-label study and doesn't involve blinding and unblinding.

5.12. Past and Concomitant Treatment

5.12.1. Previous medications/treatment

Any information of all medications (including vitamin supplementation, over the counter medications and oral herbal preparations) or non-drug treatments used within 30 days prior to signing the informed consent form and prior to the first dose of the study drug should be recorded in source documents and electronic Case Report Form (eCRF) of patients.

5.12.2. Prior Anti-Tumor Therapy

Any prior anti-tumor drugs and non-drug treatments should be recorded in source documents and eCRF of patients.

5.12.3. Concomitant medication

Any medications (including vitamin supplementation, over the counter medications and oral herbal preparations) or non-drug treatments used in the period from the first dose of the study drug to 30 days (including 30 days) after the last dose of the invstigational drug should be recorded in source documents and eCRF of patients.

5.12.3.1. Drugs Allowed to be Used

Patients can use drugs that can relieve symptoms (such as analgesics, laxatives and antiemetics) as long as they are not prohibited by the study protocol.

The drug restrictions are not applicable to sunitinib. Please refer to the approved package insert for information of sunitinib.

5.12.3.2. Prohibited Drugs and Substances

Prohibited drugs and some food are not allowed from the screening period to safety follow-up visit. Except for the study drug, anti-tumor therapies that have an inhibitory effect or potential inhibitory effect on GIST are prohibited during the study.

All patients should abide by the following criteria of prohibited drugs before randomization.

- Receive imatinib treatment within 10 days prior to the first dose of the study drug or any other anti-tumor drugs or therapies for advanced GIST.
- 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, whichever is longer) prior to the first dose of the study drug.

  For guidance of CYP3A4 enzyme inhibitor, 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 prohibited within at least 14 days prior to the first dose of the study drug.
- Known BCRP transporter substrate or inhibitor: discontinue within at least 14 days or 5 half-lives (whichever is longer) prior to the first dose of the study drug.

  For information of BCRP inhibitors and substrates, please refer to Food and Drug Administration (FDA) website: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm.

After randomization and during the study, patients randomized to the sunitinib group will follow requirements for prohibited drugs specified in the approved package insert.

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

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

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

Patients who use DCC-2618 (ripretinib, ZL-2307) should avoid the following drugs or use the following drugs with caution after discussing with the sponsor (provide updated information to study site during the study):

- Strong or moderate inhibitors of CYP3A including grapefruit juice.
- Known substrates or inhibitors of BCRP transporters and P-glycoprotein 1 (permeability glycoprotein, also known as MDR1). Please refer to the FDA’s website for inhibitors https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htmMedications dependent on CYP2C8 for their metabolism. Please refer to the Indiana University Department of Medicine website

(http://medicine.iupui.edu/clinpharm/ddis/main-table/) for guidance on these medicines.

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For patients who use any of the above drugs, any potential drug interaction with DCC-2618 (ripretinib, ZL-2307) should be closely monitored.

Please refer to the approved package insert for drug interaction of sunitinib.

5.12.4. Concomitant medical procedures

All medical procedures carried out from the first dose of the study drug to 30 days (including 30 days) after the last dose of the study drug should be recorded in source documents and eCRF of patients.

Surgical resection or palliative radiotherapy during the study treatment should be discussed with the sponsor before implementation. For patients who obtain PR, resection of residual lesions is allowed if patients have finished 12-month treatment. If the investigator considers the treatment meets the patient's best interests, after discussing with the sponsor, surgical resection or palliative radiotherapy can be carried out.

5.13. Other Precautions

To relieve potential risks of photostimulation/phototoxicity, patients should be instructed to take DCC-2618 (Ripretinib, ZL-2307), avoid strong sunlight, fluorescent lamp and other ultraviolet radiation sources during the study. For all patients who use DCC-2618 (ripretinib, ZL-2307), preventive skin care suggestions include use of SPF ≥ 30 sunscreen cream, anti-allergy moisturizer or ointment relieving dry skin, and mild skin care products containing tasteless soap and detergent.

Please refer to the approved package insert for warnings and precautions of sunitinib.

6. Study Evaluation

6.1. Screening

Screening must be carried out within 28 days prior to the first dose of the study drug to confirm that the patient meets inclusion criteria of the study. Radiographic examinations and dermatologic examinations can be carried out within 28 days prior to the first dose of the study drug. See Table 1 (Schedule of Assessments) for items to be assessed.

6.2. Re-screening

Patients can be re-screened only after obtaining the approval of the sponsor. If patients are re-screened, all screening evaluation items except tumor tissue specimens (if applicable) should be repeated. If radiographic evaluation, echocardiogram and dermatologic examination are carried out within 28 days prior to the first dose of the study drug, the examinations don’t need to repeat. Patients can be re-screened once only. If patients are re-screened, screening time window will be timed after initiating the first re-screening evaluation item.

6.3. Treatment period

After confirming that patients meet all criteria, patients will be randomized to the study. The first dose of the study drug must be administered in department on C1D1. See Table 1 (Schedule of Assessments) for study visit schedule during treatment. Patients will be taken as outpatients during treatment. All visits should be carried out in the regulated window.

Patients who discontinue treatment with the study drug must return to the department for EOT visit within 7 days after the last dose of the study drug. If the interval between the last visit before discontinuing treatment with the invstigational drug and EOT visit is over 14 days (excluding 14 days), comprehensive evaluation of items should be carried out according to Table 1 (Schedule of Assessments) at EOT visit. If the interval between the last visit before discontinuing treatment with the invstigational drug and EOT visit is not more than 14 days (including 14 days), only items that are not evaluated at the last visit need to be assessed at EOT visit.

6.4. Follow-up

Patients will be contacted by telephone 30 (±5) days after the last dose of the study drug for safety follow-up to evaluate AE, collect information of concomitant medications/other treatments and collect new information of anti-tumor therapy.

After that, patients will be contacted by telephone for OS follow-up to collect new information of anti-tumor therapy and OS data.

6.5. Lost to Follow-up

Patients will be considered lost to follow-up in the following conditions: patients cannot be contacted by telephone three times within 2 weeks after the first failure of contact and telephone contact records should be made.

6.6. Study Evaluation

Table 1 Summarizes schedule of assessments of each visit.

Unless otherwise specified, all assessments must be carried out prior to administration and in the predetermined window of visit.

Additional unscheduled safety or efficacy assessment can be carried out at any time with clinical indications to confirm the correlation between the specific findings and the study drug and/or duration of the event.

6.7. Inform Consent Process

Each patient must sign and date the specific ICF before any specific procedure of the study. ICF will follow all applicable regulations of patient protection. The ICF approved by the sponsor, institutional review board (IRB) of the study site/independent ethics committee (IEC) must be used. The investigator or designated personnel must record consent process, including

recording the date of signing the informed consent form in source documents of patients.

6.8. Distribution of Patient Number

After obtaining informed consent, a unique patient identification number (patient number) will be assigned to each patient. Please refer to the study reference manual for details of assigning patient number. If the patient receives re-screening, a new patient number will be used.

6.9. Demographics and Medical History

Demographic information must be collected during screening.

Cancer history and prior treatment history (including reasons for treatment discontinuation) should be obtained during screening. Cancer history includes:

- Known GIST histological diagnostic
- Tumor mutation status: molecular test report of patients should be collected during screening and necessary archived and/or fresh tumor tissue samples should be collected. If the molecular test report provided by patients is available, randomization stratification can be carried out according to the molecular test report and it is not required to test archived tumor tissue samples or fresh live tissues before randomization. If patients cannot provide molecular test report or the report is unusable or insufficient, an archived tumor tissue sample or fresh live tissue should be tested to confirm KIT or PDGFRA mutation status prior to randomization. The central laboratory will analyze tumor tissues to identify mutation of KIT or PDGFRA.
- All prior anti-cancer therapy regimens, including:
    - Surgery (including tumor tissue samples): including date of resection surgery, site and range of resection (such as, resection of tumor tissue samples, R0, R1, or R2 only)
    - Prior imatinib treatment: including treatment starting date, dose and dosing schedule, treatment reason (such as adjuvant therapy of metastatic disease), best response, progressive disease date, date and reasons of treatment discontinuation.
    - Radiation therapy: including treatment site, total dose, treatment date and response
    - Other treatment procedures, such as radiofrequency ablation (if applicable)

Molecular test report with KIT/PDGFRA mutation status should be provided to the investigator before randomization. If molecular test report is unusable or insufficient, an archived tumor tissue sample or fresh live tissue should be tested to confirm mutation status prior to randomization.

The investigator must obtain medical history of each patient during screening, including any obvious adverse conditions and diseases during and before obtaining informed consent. It is necessary to evaluate whether patients have any unqualified medical conditions specified in the inclusion and exclusion criteria based on medical history assessment. Medical history

should include complete review of system, past medical history, surgery history and any allergy history. Ongoing signs of disease should be considered as comorbidities: if possible, starting date of these comorbidities should be recorded.

6.10. Effectiveness

6.10.1. Imageological examination

Enhanced pelvic, abdominal and chest CT scan of all patients will be carried out according to Table 1 (Schedule of Assessments) for tumor efficacy assessment. Radiographic examination prior to informed consent can be used for screening evaluation as long as the examination is performed within 28 days prior to the first dose of the study drug and meets requirements of the study.

Imageological examination can be performed within the corresponding study visit ± 7 days during the study. After C7D1, based on the investigator's assessment, any initially indicated PR or CR should be confirmed ≥ 4 weeks after start of response. MRI scans of the abdomen/pelvis and CT scan without contrast of the chest can be used for patients who are allergic to radiographic contrast media or at the Investigator's discretion based on the best interest of the patient after discussion with the Sponsor.For each patient, the same evaluation technology should be adopted during the whole study, and the evaluation technology could not be changed unless the investigator's consideration of safety risk. Ultrasound scan should not replace CT scan.

Copies of all imageological examinations must be obtained and sent to the independent imaging supplier designated by the sponsor. The independent imaging supplier will assess imaging quality and be responsible for institutional independent radioloicy review.

Independent imaging supplier must ensure institutional independent radiologic reviewers are blinded to investigator's assessment.

Independent radiologic reviewers and the investigator will evaluate tumor response using "RECIST v1.1-GIST-specific Criteria" (see Section **Error! Reference source not found.**). Response confirmed by investigators will be recorded in the eCRF. Assessment data obtained by the independent radiologic review (IRR) will be used for analysis of the primary endpoint.

Confirmation of progressive disease: If the independent radiologic reviewer confirms progressive disease using "RECIST v1.1-GIST-specific Criteria", the patient must discontinue the invstigational drug and receive EOT visit, safety follow-up, and OS follow-up.

Confirmation of absence of progressive disease: if institutional independent radiologic reviewers confirm there is no progressive disease, the patient will continue to receive the study drug, unless there are medical needs requiring discontinuation of the study drug (that is, rapid progression or clinical worsening). If investigators confirm progression according to clinical worsening, imageological examination should be performed and reviewed by institutional independent radiologic reviewers to confirm whether the patient has progression. Basis for

confirming progression based on clinical worsening should be recorded in source documents and eCRF of patients. If the investigator confirms progressive disease according to "RECIST v1.1-GIST-specific Criteria", the investigator should wait for assessment and confirmation by the independent radiologic review and then terminate the patient's treatment. If the investigator doesn't hope to confirm by the independent radiologic review or hopes to terminate the patient's treatment according to progressive disease based on "RECIST v1.1-GIST-specific Criteria" before obtaining results of the independent radiologic review, it is necessary to discuss with the sponsor.

Radiographic examination of patients of various treatment groups should be performed according to the predetermined time and cycle will not be influenced by suspension or delay of treatment with the study drug. If the patient discontinues treatment for reasons other than progressive disease, death, withdrawal of consent and lost to follow-up, the patient should receive radiographic examination for tumor assessment according to the specified time interval after treatment withdrawal until progressive disease based on "RECIST v1.1-GIST -specific Criteria" or initiation of new anti-tumor therapy.

6.10.2. Overall survival follow-up by telephone

All patients will be followed up until withdrawal of consent or death for any reason. After safety follow-up visit, patients will be contacted once every 2 months (± 10 days) to collect new information of anti-tumor therapy and OS data.

6.11. Safety

Safety evaluation will be based on changes in physical examination, ECOG PS and vital signs from baseline, ECG, LVEF based on echocardiogram, dermatologic examination, clinical laboratory test and AE reports.

6.11.1. Physical examination

A comprehensive physical examination will be done during screening. Comprehensive physical examination includes review of the following system: head/neck/thyroid gland, eye/ear/nose/throat, respiratory, cardiovascular, lymph node, abdomen, skin, muscle and musculoskeletal and nervous system. If medically indicated, breast, anorectum and genitals will be examined. All other visits and examinations will be arranged according to clinical findings and/or patients' chief complaints. After screening, any clinically significant abnormalities in physical examination should be reported as AE.

6.11.2. ECOG performance status

ECOG PS will be evaluated according to Table 1 (Schedule of Assessments)[25]. ECOG PS can be assessed before OR after administration.

6.11.3. Vital sign, weight and height

Vital signs, height and weight will be measured according to Table 1 (Schedule of

Assessments). Vital sign assessment involves sitting blood pressure, pulse, respiratory rate and body temperature. These parameters will be assessed after 5 minutes of rest (sitting or supine position).

6.11.4. Electrocardiogram

12-lead ECG will be carried out according to Table 1 (Schedule of Assessments).

All ECG examination must follow the following regulations:

- All standard digital electrocardiogram must be carried out at least 15 minutes after the patient has a rest.
- ECG examination must be carried out before administration of study drug.

Heart rate and the following ECG intervals will be entered into the database:

- PR interval
- QT, QTcB and Fridericia-corrected QT interval (QTcF) ($QTcF = QT/(60/\text{heart rate})^{1/3}$)
- QRS duration

6.11.5. Echocardiogram

Echocardiography will be performed according to Table 1 (Schedule of Assessments). Echocardiogram before informed consent can be used for screening assessment as long as the echocardiogram is performed within 28 days prior to the first dose of the study drug. LVEF should be recorded in source documents and eCRF of patients.

6.11.6. Dermatologic examination

All patients will receive evaluation of skin damages by dermatologist according to Table 1 (Schedule of Assessments) and clinical indications, especially squamous cell carcinoma of skin, actinic keratosis and keratoacanthoma. Examination site should include the whole skin. Dermatologic examination meeting standard of the study protocol performed prior to informed consent can be used for screening evaluation as long as the examination is performed within 28 days prior to the first dose of the study drug. Any new or changed skin damages during treatment must be recorded in source documents and eCRF of patients. If patients are suspected with squamous cell carcinoma of skin or keratoacanthoma, diagnosis should be confirmed by a certificated pathologist through biopsy skin at study site. Please refer to Section 7.9 for more information of diagnosis and treatment of squamous cell carcinoma of skin, actinic keratosis and keratoacanthoma (regarded as AESI).

6.11.7. Hepatitis B, Hepatitis C and HIV Antibody Testing

Hepatitis B and C examination in the screening period: HBsAg, anti-HBs, HBeAg, anti-HBe and anti-HBc and anti-HCV antibody examination will be performed first. If results of five indicators of hepatitis A are abnormal, HBV DNA quantitative test should be performed; if anti-HCV antibody positive, HCV RNA quantitative test should be performed. For patients with abnormal baseline HBV DNA, HBV DNA quantitative test should be performed once every 2 weeks during the trial and at the end of study.

HIV antibody test should be carried out in the screening period.

6.11.8. Clinical laboratory tests

Blood and urine samples will be collected and analyzed according to Table 1 (Schedule of Assessments). All blood samples must be collected when the patient is in a sitting or supine position. If laboratory test abnormality is clinically significant, it should be reported as AE (Section 7.7.1). All laboratory test results must be graded according to toxicity definition in Common Terminology for Adverse Events of National Cancer Institute (NCI CTCAE), v5.0.

Items of safety laboratory tests refer to Table 1111.

Table 11: Safety laboratory tests

Blood biochemistry	**Blood routine**	**Routine urine test**
Blood glucose Blood urea nitrogen/urea Creatinine Sodium Potassium Calcium Magnesium Phosphonium Bilirubin total and Bilirubin direct Alkaline phosphatase Glutamic-oxaloacetic transferase Alanine transaminase Lactate dehydrogenase Total protein Albumin Creatine phosphokinase Globulin Triglyceride Lipase	Haemoglobin Platelet White blood cells Reticulocyte Classification (absolute count): • Neutrophil • Lymphocyte • Monocyte **Coagulation tests**[1] Activated partial thromboplastin time Pro-thrombin Time International Normalized Ratio	Protein urine Urine occult blood Specific gravity Urine ketone body Urine Glucose
Thyroid test		
Thyroid stimulating hormone (TSH) Free triiodothyronine (FT3)		

Blood biochemistry	Blood routine	Routine urine test
Free thyroxine (FT4)		

1. For patients who take anticoagulant, test will be carried out according to Table 1 (Schedule of Assessments). If the dose of anticoagulant changes during the study, monitoring of coagulation function should be increased if clinically suitable.

6.11.9. Pregnancy test

To exclude pregnancy in women of childbearing potential, serum β-hCG test will be carried out at screening. As shown in Table 1 (Schedule of Assessments), urine pregnancy test will be completed at all other visits. Pregnancy test is not required in female patients without fertility. These patients refer to postmenopausal (amenorrhea ≥ 12 months and follicle stimulating hormone [FSH] ≥ 40 mIU/mL) women or women with proof document of total hysterectomy or total ovariectomy.

6.11.10. Contraception and contraceptive measures

6.11.10.1. Contraception

Influence of DCC-2618 (Ripretinib, ZL-2307) on sperm, conception, pregnancy and breastfeeding is unknown. Patients who receive DCC-2618 (ripretinib, ZL-2307) in the study should agree to take contraceptive measures. Effective contraceptive measures should be taken from at least 14 days before the first dose of DCC-2618 (ripretinib, ZL-2307) until 104 days after the last dose of DCC-2618 (ripretinib, ZL-2307).

Patients who use sunitinib in the study should agree to take effective contraceptive measures according to the approved package insert.

Female patients and female partners of male patients who use DCC-2618 (ripretinib, ZL-2307) should not plan to become pregnant during the study until 104 days after the last dose of DCC-2618 (ripretinib, ZL-2307) or the last dose of sunitinib.

If it is uncertain that whether female or male with fertility will reliably follow requirements for contraception, the patient should not be included into the study.

6.11.10.2. Pregnancy

Patients who receive DCC-2618 (ripretinib, ZL-2307) must inform the investigator of any pregnancy during the study treatment and within 104 days after the last dose of DCC-2618 (ripretinib, ZL-2307). Patients who use sunitinib must inform the investigator of any pregnancy during the study treatment.

If female patient becomes pregnant during the study, treatment with the study drug should be discontinued immediately forever. If female partner of male patient becomes pregnant during the study, the patient must inform the investigator immediately. Male patients must promise to take acceptable contraceptive measures during the study until 104 days after the last dose of

CC-2618 (ripretinib, ZL-2307) or the last dose of sunitinib (to ensure fetus is not in contact with the study drug). The investigator must inform the sponsor within 1 work days after the study site is aware of pregnancy of patients (or partners).

If the patients is receiving DCC-2618 (ripretinib, ZL-2307) treatment, the patient or female partner of male patient must be followed up until end of pregnancy. If informed consent is obtained, infants must be followed up until 1 year after birth. Pregnancy itself is not an AE.

6.11.11. AEs

All AEs will be evaluated, recorded and reported according to Good Clinical Practice (GCP) of the International Conference on Harmonization (ICH). Chapter **Error! Reference source not found.** summarizes the definition, collection period, evaluation criteria, recording, grading and reporting procedure of AEs.

6.11.12. Safety follow-up

AE follow-up should be carried out in all patients 30 (±5) days after the last dose of the study drug to collect information of concomitant medications/other treatments and collect new information of anti-tumor therapy.

6.12. Pharmacokinetics

6.12.1. Sampling

At visits listed in Table 1 (Schedule of Assessments), blood samples will be collected from patients who use DCC-2618 (ripretinib, ZL-2307) to determine the concentration of DCC-2618 (ripretinib, ZL-2307) and its metabolite DP-5439. Pre-dose blood samples must be collected within 60 minutes prior to administration and post-dose blood samples must be collected within the specified time point ± 30 minutes. If the sponsor requires, unscheduled PK samples can be collected when new, suspicious, and treatment-related AEs occur.

Detailed information of sample collection, processing, storage and shipment will be provided in an independent specific laboratory manual of the study protocol.

6.12.2. Sample evaluation

Descriptive statistics and summary of drug concentration at relevant time points will be carried out according to plasma concentration of DCC-2618 (ripretinib, ZL-2307). If necessary, pharmacokinetic data of this study will be included into population PK analysis with industrial standard software. Population PK report will be drafted independently and not taken as the appendix of the study report.

6.13. Biomarkers and pharmacodynamics

6.13.1. Sample collection

Tumor tissues and blood samples will be collected according to Table 1 (Schedule of Assessments). Laboratory manual will be provided to describe detailed information of sample

collection, processing, storage and shipment.

6.13.2. Sample evaluation

6.13.2.1. Tumor tissue samples

Necessary archived and/or fresh tumor tissue samples will be collected at screening. If archived tumor tissues cannot be used or are insufficient for mutation analysis, fresh tumor tissue samples should be collected. The central laboratory will analyze tumor tissues to identify molecular mutation of KIT or PDGFRA.

All patients (optional): Tumor tissue samples can be collected at EOT visit and/or from patients who are receiving medical procedures, including resection of metastasis in the study, or from patients who have progressed (if the patient agrees). These samples will be used for further molecular test of cancer during receiving the study drug.

6.13.2.2. Blood sample

Blood samples will be collected from patients who receive DCC-2618 (ripretinib, ZL-2307) and sunitinib treatment according to Table 1 (Schedule of Assessments) and analyzed by the central laboratory to evaluate mutation status of KIT or PDGFRA as well as longitudinal frequency change of its ctDNA.

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

7.1. Adverse Events (AEs)

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

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

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

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

7.2. Severity Assessment

The Investigator must determine and record the severity of all serious and non-serious AEs. The NCI-CTCAE, Version 5.0, must be used for grading the severity of AEs (cancer therapy evaluation program website: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0/).

The severity of an AE that does not appear in the CTCAE scale must be determined according to Table 122.

Table 122: National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0 Severity Grading Scale

Grade 1 (mild)	Asymptomatic or only mild symptoms; clinical or diagnostic observations only; intervention not indicated;
Grade 2 (moderate)	Minimum, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
Grade 3 (severe)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
Grade 4 (life threatening)	Life-threatening results; urgent intervention indicated.
Grade 5 (death)	Death related to AE.

7.3. Causality assessment

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

Relationship to study drug administration must be determined by the Investigator according to the following criteria in Table 13.

Table 133: Relationship to Study Drug Criteria

The investigator must evaluate and provide the causal relationship between adverse event and the study drug. The following table 11 can be used as reference for caualtiy assessment.

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

For the purpose of safety analysis, all adverse events that are classified to be possibly related

to the study drug will be regarded as treatment-related events.

7.4. Study Drug Action Taken

The investigator must clarify measures to the study drug due to AE. Measures taken must be classified according to categories shown in Table 144.

Table 144: Classification for Study Drug Action Taken with Regard to an Adverse Event

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

7.5. Adverse Event Outcome

An AE must be followed until the Investigator has determined and provided the final outcome. The outcome must be classified according to the categories shown in Table 15.

Table 155: Classification of adverse event outcome

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

The investigator should continue to follow up any adverse event that has not recovered at the last visit of the study until there is no clinical indications and the patient start new anti-tumor theropy, whichever occurs first; and 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.

7.6. Treatment measures on AEs

The Investigator must ensure adequate medical care is provided to patients for any AEs. In addition, the Investigator must describe whether any treatment was given for the AE. "Yes" is used if any treatment was given in response to an AE and may include treatments such as other medications,

hospitalization, surgery, or physical therapy. "No" indicates the absence of any kind of treatment for an AE.

7.7. Additional Considerations on Adverse Events

7.7.1. 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). Once the diagnosis is confirmed with the follow up information, the symptoms and sign should be replaced with diagnosis accordingly. 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 study drug, such as drug discontinuation or treatment termination.

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

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

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

7.8. Definition of Serious Adverse Event(SAE)

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

• Results in death (regardless of cause, that occurs during participation in the study or occurs after participation in the study and is suspected of being a delayed toxicity due to administration of the study drug)

• Is life threatening (an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe)

• Requires inpatient hospitalization or prolongation of existing hospitalization

• Results in persistent or significant disability/incapacity

• Results in congenital anomaly/birth defect

• Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes (i.e. allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

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)

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

The following AEs are considered AESIs:

- Squamous cell carcinoma of skin
- Actinic keratosis
- Keratoacanthoma

7.10. Adverse Events Reporting Period

The AE (including SAEs and AESIs) reporting period begins from the time that the patient provides informed consent through and including 30 days after the last dose of the study drug, or until a new anti-tumor therapy is initated, which occurs first. For any SAEs or AESIs occurring after this reporting period, it will be reported only when a causal relationship between the SAEs or AESIs and study product is suspected by the study drug.

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

Each patient must be carefully monitored for the development of any AEs. This information must be obtained in the form of non-leading questions (e.g. “How are you feeling?”) and from signs and symptoms detected during each examination, observations of study personnel, and spontaneous reports from patients. All AEs (serious and non-serious) spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures must be recorded.

When possible, signs and symptoms indicating a common underlying pathology must be noted as 1 comprehensive event. Accompanying signs or symptoms (e.g. abnormal laboratory values) must not be reported as additional AEs. If a diagnosis is unknown, one or more symptoms may be reported as separate AEs. If an underlying diagnosis is subsequently determined for the reported symptom(s), then the reported symptom(s) term(s) must be revised to be “attributed” or “due” to the diagnosis.

All SAEs and AESIs that occur within the reporting period, regardless of causality, must be reported by the Investigator as applicable to competent authoridy, Ethics Committe or sponsor pharmacovigilance team **within 24 hours** from the point in time when the Investigator becomes aware of the SAE or AESI. For reporting purpose, the following procedures must be followed.

The investigator should send completed, signed and dated SAE Report Form to (within 24 hours of awareness): the public email mailbox of Drug Safety Department in Zai Lab: saereporting@zailaboratory.com.

(1) 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.

When in the opinion of the investigator when clinical benefit is sustained even after the clinical trial is closed, treatment with DCC-2618 (Ripretinib, ZL-2307) will be continued until disease progression, death, intolerable toxicity or patient's desire to withdrawal. For those patients, only SAEs will be collected 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.

- Processing of Death Cases

All deaths occurring during the study, including within 30 days after the last dose of study drug, during the safety follow-up period of the last dose of study 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 cannot be 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 or is the main cause of death, as appropriate.
- Death with unknown causes must be reported as SAE. The cause of death should be clarified with every effort in follow-up activities. Autopsy is crutial 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.

- Serious Unexpected Adverse Reactions (SUSARs)

If drug-related serious unexpected adverse reactions (SUSARs) occur, the sponsor or the authorized personnel designated by the sponsor will ensure expedited reporting to appropriate regulatory authorities or other investigators taking part in this study. In addition, the sponsor or the authorized personnel designated by the sponsor will be responsible for reporting SUSARs to the ethics committee.

- Pregnancy

  Effective contraception is required for both male and female subjects of childbearing potential who are treated with DCC-2618 (Ripretinib, ZL-2307) during the trial and for 104 days after discontinuation of study drug. If a subject is found to be pregnant following initiation of study treat, the study 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 104 days after the last dose of study drug, the investigator should be informed immediately. The pregnancy must be recorded on "Pregnancy Reporting Form" and reported by the investigator to the Sponsor via email within 24 hours of becoming aware of the event. 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 miscarriage or therapeutic miscarriage [any congenital anomaly detected in the miscarriage fetus], stillbirth, neonatal death, or birth defect and any congenital anomaly), 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 medication errors

The adverse events or at risk scenairos including drug abuse, misuse, overdose and medical errors should be reported to the sponsor.

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

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

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

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

•The dispensing, administration and/or use of the unassigned study drug.

•The administration and/or use of an expired study drug.

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

AEs or SAEs associated with drug abuse, misuse, overdose, or medication error must be reported as appropriate (add appropriate section for reporting of AE)

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

8. Patient withdrawal and replacement

8.1. End of treatment

Patients may withdraw from treatment with the study drug for any reasons at any time without providing any reasons and will not have any punishment or damages. If clinically required, the investigator may terminate treatment with the study drug for the patient at any time. The main reason for termination or discontinuation of the study drug should be confirmed according to the following classification:

- Clinical progression
- Disease progression confirmed by institutional independent radiologic review

- AE
- The patients request withdrawal from the treatment
- Death
- Lost to Follow-up
- Investigator's decision
- Pregnancy
- Termination of the study by the sponsor

If the patient requests to withdraw from treatment, the investigator should try to contact the patient to confirm reasons for withdrawal and ask the patient to return to study site to receive EOT visit and safety follow-up. If the patient withdraws from the study for any reasons other than “requesting withdrawal”, EOT visit, safety follow-up visit and OS follow-up visit should be carried out. Patients should return all used, partially used and unused study drugs and bottles.

8.2. End of Study

The main reason for termination or withdrawal form the study should be confirmed according to the following classification:

- Death
- Lost to Follow-up
- Termination of the study by the sponsor
- Patients will withdraw from the study

8.3. Patient withdrawal and replacement

Patients will be not substituted in the study.

9. Statistical Consideration

9.1. Determination of sample size

This study will bridge foreign clinical trial (study INTRIGUE) to prove the efficacy of the investigational drug DCC-2618 (ripretinib, ZL-2307) is consistent in foreign population and Chinese population. In the study, no statistical test hypothesis is specified in advance. Statistical significance test for efficacy endpoint and multiplicity correction for multiple analysis populations will not be performed.

Approximately 98 subjects will be enrolled into the study and randomized to a test group and a control group in a 1:1 ratio. The sample size eatimation will be based on the same study hypothesis as foreign, that is, median progression-free survival (mPFS) is 9 months in the test

group and 6 months in the control group. Hazard ratio (HR) of the test group to the control group is 0.667. If the study keeps ≥50% of the overall effect size of study INTRIGUE, that is, point estimate of HR should be ⩽ 0.833, it will be considered that results of this study are consistent with those of study INTRIGUE. If 58 cases of PFS events occur, a 80% probability will be obtained and athe conclusion of consistency will be drawn with a probability of 80%. Assumeing the subjects annual drop-out rate of subjects of the total study population is 5%, approximately 98 subjects (49 for the test group and the control group, respectively) are enrolled within 7 months and followed up for 7 months, and 58 cases of PFS events will occur. Main Primary analysis based on ITT will be carried outperformed when 58 cases of PFS events occur and it is estimated that the data cutoff of the analysis will be 7 months after completing enrollment.

In population with KIT exon 11 mutation, it was assumed in the foreign study that mPFS of the test group was 9 months and mPFS of the control group was 5 months, and HR of the test group to the control group was 0.556. If the study keeps ⩾a 50% and of the overall effect size of study INTRIGUE in population with KIT exon 11 mutation, that is, point estimate of HR should be ⩽ 0.778, it will be considered that results based on KIT exon 11 mutation population in this study are consistent with those in study INTRIGUE. If 26 cases of PFS events occur in population with KIT exon 11 mutation, the conclusion of consistence with study INTRIGUE can be drawn with a probability of 80%.

9.2. Study Endpoints

9.2.1. Primary endpoints

The independent radiologic review will assess PFS according to “RECIST v1.1-GIST-specific Criteria ” (Appendix 16.1). “RECIST v1.1-GIST-specific Criteria” assessment criteria include:

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

9.2.2. Secondary endpoints

9.2.2.1. Effectiveness

- ORR (confirmed CR + confirmed PR) based on independent radiologic review
- Disease control rate (DCR) at months 6, 9 and 12, assessed by independent radiologic review
- PFS assessed by the investigator according to "RECIST v1.1-GIST-specific Criteria"
- Overall survival (OS)

9.2.2.2. Safety

- Incidence of treatment emergent adverse event (TEAE), adverse event of special interest (AESI) and serious adverse event (SAE); severity of adverse event will be assessed (based on NCI CTCAE 5.0);
- Incidence of adverse events resulting in dose adjustment of the study drug or termination of the study;
- Changes in each parameter like ECOG score, vital signs, electrocardiogram, left ventricular ejection fraction, dermatologic examination and laboratory indicators from baseline.

9.2.2.3. Pharmacokinetic characteristics

Descriptive statistics and summary of drug concentration at relevant time points will be carried out according to plasma concentration of DCC-2618 (ripretinib, ZL-2307). If necessary, pharmacokinetic data of this study will be included into population PK analysis with industrial standard software. Population PK report will be drafted independently and not taken as the appendix of the study report.

9.2.3. Exploratory endpoint

- KIT/PDGFRA mutation of tumor tissues at baseline and specific time points (e.g., resection of metastasis or progressive disease during the study).
- KIT/PDGFRA mutations and mutant allele frequency at baseline and the treatment effect of DCC-2618 (ripretinib, ZL-2307) on KIT/PDGFRA mutant allele frequency (MAF).

9.3. Analysis Population

The following populations will be used for analysis: all patients intent-to-treat (ITT) population, KIT exon 11 mutation intent-to-treat (Ex11 ITT) population, safety population, PK population, all patients per-protocol (PP) population and KIT exon 11 mutation per-protocol (Ex11 PP) population.

ITT population is defined as all randomized patients. Patients in the population will be analyzed according to treatment they will receive.

KIT exon 11 mutation intent-to-treat (Ex11 ITT) population is defined as all patients with KIT exon 11 mutation at randomization. Patients in the population will be analyzed according to

treatment they will receive.

Safety analysis population is defined as all subjects who were randomly assigned and received at least one dose of study drug. Safety population will be used for all safety analyses and treatment assignment will be based on the actually received initial study treatment.

PK population will include all randomized subjects who have received at least one dose of DCC-2618 (ripretinib, ZL-2307) and have at least a non-missing plasma PK concentration report of DCC-2618 (ripretinib, ZL-2307) and DP-5439.

PP population is defined as all patients in ITT population who have at least one tumor assessment after baseline, meet all inclusion criteria, don't violate any exclusion criteria and don't have any significant study protocol violation/deviation that are considered to influence the integrity of the study. Efficacy analysis in the PP population is supportive and the analysis in treatment groups will be based on the actually received treatment. Patients who violate the study protocol and excluded from the PP population will be identified and recorded before locking the database.

KIT exon 11 mutation per-protocol (Ex11 PP) population is defined as all patients in Ex11 ITT population who have at least one tumor assessment after baseline, meet all inclusion criteria, don't violate any exclusion criteria and don't have any significant study protocol violation/deviation that are considered to influence the integrity of the study. Efficacy analysis in the Ex11 PP population is supportive and the analysis in treatment groups will be based on the actually received treatment. Patients who violate the study protocol and excluded from the Ex11 PP population will be identified and recorded before locking the database.

Note: If a patient has exon 11 mutation with 1) exon 9 and/or PDGFRA mutation, the patient will be considered with exon 11 mutation at randomization. Mutation type of the patient will be defined according to a mutation with a higher MAF if the patient has mutation allele frequency (MAF) data; 2) other KIT exon mutation, the patient will be considered with exon 11 mutation at randomization.

9.4. Processing procedures of missing data, unused data and false data

Calculation of interpolating or missing date is shown in Table 166. Interpolate AE end date to calculate the duration of AE.

Table 166: Calculation of some or missing date

Variables	Missing Day	Missing date and month	Missing date, month and year
Date of the last treatment/initial diagnosis	Assigned 1 day	Please assign January 1 if before the date of informed consent, or else use the date of informed consent	Missing (don't interpolate)
AEs/Starting date	Assign the first day of the	Assign January 1, unless	Assign the date of the

	month, unless the first dose of the study drug is given in this month. Or else, assign the date of the first dose of the study drug or end date of AE (if not missing), whichever occurs first.	the first dose of the study drug is given this year. Or else, assign the date of the first dose of the study drug or end date of AE (if not missing), whichever occurs first.	first dose of the study drug.
The end date of adverse event	Assign the last day of this month or study end date, whichever occurs first.	Assign December 31 or study end date, whichever occurs first.	If the event continues, end date will be left blank. Otherwise, study end date was to be assigned.

9.5. Statistical Method

9.5.1. General methods

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

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

Medical history, AEs and concomitant treatment procedures will be coded with Medical Dictionary for Regulatory Activities (MedDRA). Past and concomitant medications will be coded according to the World Health Organization Drug Dictionary.

Unless specified otherwise, Ex11 ITT population and ITT population are used for efficacy analysis (primary endpoint and secondary endpoint) and safety population is used for safety analysis.

9.5.2. Patients disposition

Dispositionof all patients entering the study (patients who sign the informed consent form of the study and meet the inclusion criteria and don't meet the exclusion criteria) will be summarized. The number of patients in each population (safety, PK, Ex11 ITT, ITT, Ex11 PP, PP, if applicable) and the number of patients excluded from each population will be displayed. The number and proportionof patients who completethe study, as well as those who discontinue the studywill be summarized along with the reason for discontinuation.

9.5.3. Demographic data and baselinecharacteristics

Demographic and baseline characteristics (including recurrence risk evaluation at enrollment) will be summarized.

Medical history will be summarized for the safety population.

9.5.4. Extent of exposure

Total subjects who receive treatment with the investigational drug will be summarized with n and percentage. Moreover, continuous descriptive statistics will be used to display number of treatment cycles subjects received. These analyses will be performed for the safety population.

9.5.5. Efficacy analysis

9.5.5.1. Primary endpoint: progression-free survival

The primary endpoint PFS is defined as the time interval from randomization to the earliest documented evidence of progressive disease based on assessment of the independent radiology review or death due to any causes. PFS analysis in the ITT population will be stratified by the randomization stratification factors (KIT exon 11 mutation; KIT exon 9 mutation; other (KIT/PDGFRA WT or other KIT [lacking exon 9 or 11]/PDGFRA mutation). Survival curve of different treatment groups will be plotted with KM method and the median progression-free survival (mPFS) and its 95% CI of different groups will be calculated. Under a two-sided significance level of 0.05, stratified log-rank test will be adopted to compare difference in survival curve between the two groups. Point estimate of hazard ratio will be obtained by stratified Cox regression model and relevant 95% CI will be calculated with Wald method. Randomization stratification factor is stratification factor and treatment factor is the covariant.

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

ITT population will be used as the primary analysis population in this analysis while the PP

population as supportive analysis population. Sensitivity analysis of progression-free survival will be performed, which will be further described in SAP.

9.5.5.2. Secondary efficacy endpoints

9.5.5.2.1. Analysis of objective response rate

ORR is defined as the proportionof patients, which is confirmed as CR or PR, based on independent radiology review. ITT population will be used as the primary analysis population in this analysis while the PP population as supportive analysis population. Patients with unknown or missing response will be considered non-response, that is, they will be included in the denominator when calculating proportion. Rate difference of objective response rate (ORR) between treatment groups with95% CI will be calculated with stratified Miettinen and Nurminen and statistical test will be performed

9.5.5.2.2. Overall survival

OS is defined as interval, the time from randomized allocation to patient death because of any cause. Surviving patients or those lost to follow-up will be censored on the contact day of the last assessment. Model similar to that for PFS analysis will be used for OS analysis.

9.5.5.2.3. Disease control rate

Disease control is defined as patients who obtained CR, PR or SD. DCR will be summarized according to n and proportion. Rate difference of disease control rate (DCR) between treatment groups and 95% CI will be calculated with stratified Miettinen and Nurminen and statistical test will be performed.

9.5.5.2.4. Investigator-assessed progression-free survival

Investigator-assessed PFS is defined as the time interval from randomization to the earliest documented evidence of progressive disease based on assessment of the investigator or death due to any causes. Differences between treatment groups will be assessed with the same method as the primary endpoint.

9.5.6. Safety Analysis

9.5.6.1. AEs

AEs in the safety population will be summarized with the number of events and proportionof patients according to system organ class (SOC) and preferred term. All tables will only include TEAE. “Treatment emergent” is defined as any AEs occurring during the first dose of the investigational drug and up to 30 days after the last dose of the investigational drug. However, the listing will include all AEs collected.

Toxicity grade of AE will be classified with NCI-CTCAE V5.0 (See Table 12). If a patient has the same SOC or preferred term evet for several times, only the most severe event will be

summarized in the tables for that SOC and preferred term. AEs grade ≥ 3 will be summarized. Missing toxicity grade will not be imputed.

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

Formal hypothesis test of incidence of AE will not be performed.

9.5.6.2. Eastern Cooperative Oncology Group Performance Status

Descriptive statistics will be provideded and baseline value, value after baseline and changes in value from baseline will be summarized by time points. Formal hypothesis test will not be performed.

9.5.6.3. Vital signs

Continuous descriptive statistics will be provided and assessment results will be summarized overall by time points. In addition, changes in continuous parameters from baseline will be summarized. For categorical parameters, n and proportionwill be presented. Formal hypothesis test will not be performed.

9.5.6.4. Echocardiogram

Continuous descriptive statistics will be provided and assessment results will be summarized overall by time points. In addition, changes in continuous parameters from baseline will be summarized. For categorical parameters, n and proportion will be presented. Formal hypothesis test will not be performed.

9.5.6.5. Dermatologic examination evaluation results

Descriptive statistics will be provided for summary of evaluation results of dermatologic examination. Formal hypothesis test will not be performed.

9.5.6.6. Clinical laboratory parameters

Continuous descriptive statistics will be provided and assessment results will be summarized overall by time points. In addition, changes in continuous parameters from baseline will be summarized. For categorical parameters, n and proportion will be presented. Formal hypothesis test will not be performed.

9.5.7. Pharmacokinetic analysis

Plasma concentration of DCC-2618 (ripretinib, ZL-2307) and its metabolite DP-5439 will be summarized by descriptive statistics. If the dose changes, plasma concentration can be summarized by dose level.

9.5.8. Biomarkers and pharmacodynamics analysis

Observe baseline KIT and PDGFRA mutation in plasma and features of mutation allele frequency change during the study

The Mann-Whitney U test will be used to analyze statistical difference between treatment groups in terms of treatment effectof DCC-2618 (ripretinib, ZL-2307) and sunitinib on mutation frequency tested using ctDNA at all time points. Formal hypothesis test will not be performed.

9.5.9. Procedures to report deviations from the original statistical plan

All information of deviation from source SAP will be provided in the final clinical study report.

10. Quality Control and Assurance

10.1. Monitoring visit at each study site

The sponsor or its representative will periodically carry out monitoring visit during the study to ensure the study is in compliance with the study protocol and ICH GCP requirements. The monitor will review source documents to ensure data recorded in the eCRF are accurate. The investigator and the study institution will allow the sponsor's monitor or designated personnel and corresponding regulators to directly access to source documents to implement validation.

Study site may receive IRB/IEC review, and/or quality assurance audit by the sponsor or cooperative company of the sponsor or representative company of the sponsor, and/or inspection by corresponding regulators.

What's more, the investigator and other relevant personnel should invest enough time in the procedure during monitoring visit and potential audit or inspection.

10.2. Compliance of the study protocol

The investigator should conduct the study in compliance with the study protocol provided by the Sponsor and obtain the approval/assenting view of IRB/IEC and corresponding regulatory authorities. The protocol should not be changed without the unite approval of the investigator and sponsor. Written approval/assenting view of IRB/IEC and corresponding regulators should be obtained before implementing changes to the study protocol, unless changes that must be made to eliminate direct harm to patients. If applicable regulator allows, IRB/IEC can provide expedited review and approval/assenting view for minor changes in the ongoing study if IRB/IEC approval/assenting view has been obtained. The sponsor must ensure all changes to the study protocol are submitted to regulatory authorities according to regulatory requirements.

If it is necessary to deviate from the procedure specified by the study protocol due to other unexpected conditions, the investigator must discuss with the sponsor (and IRB, IEC, as required) to confirm appropriate action steps that can be taken.

Study site must record all protocol deviations in corresponding source documents of patients. Study site must inform the sponsor (and IRB, IEC, as required) of any major deviations. Major protocol deviations include but are not limited to behaviors involving fraud or misconduct, increasing risks to patients' health or interpretations confusing the main study assessment result.

11. Data handling and record storage

11.1. Electronic case report form

The sponsor or designated personnel will provide security access rights of electronic data capture program to study sites and carry out adequate training of the program to make personnel of study sites able to enter or change information of the responsible patients in the eCRF.

The eCRF should be filled out for each randomized patient. 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. It must be clarified in source documents that prove eCRF data that patients have participated in the study. In addition, study procedure, AE, other observation results, date of patient status and detailed information should be recorded.

The investigator or designated representative should fill out eCRF as soon as possible after collecting information.

Audit tracing results will show identification information of users and any changed date and time. The eCRF should be signed by investigator in an electronic form to prove data in the eCRF (including any changes in the eCRF) are correct, which will be used to support the final data admitted by the patients charged by the investigator.

A completed 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. Recording storage

To make it convenient for regulatory authorities or the sponsor to carry out assessment and/or review, investigator must agree to retain the identity (including adequate connective information of records, e.g., the connect between an eCRF and hospital record) of all patients, all original signed ICFs, eCRF, SAE forms,source documents, detailed records of treatment management and relevant correspondence proof documents (e.g., letters, minutes and telephone reports). The investigator should retain records according to ICH, local regulations or regulations in the clinical study protocol, whichever is longer.

If the investigator cannot keep study archives to the specified time limit for some reasons (such as retirement and transfer), it is necessary to notify the sponsor in advance. Study records should be transferred to the acceptable personnel designated by the sponsor, e.g., another investigator, other institutions or the sponsor. The investigator should obtain written permission of the sponsor before destroying any records, even if the retention timeline has passed.

12. Ethics

12.1. Ethical implementationof the study

The study will be carried out according to "ethical principles for medical research involving human subject" in the *Declaration of Helsinki* of World Medical Association[26].

In addition, the study will be conducted according to the study protocol and ICH GCP.

12.2. Subject information and informed consent

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

ICF must comply with ICH GCP requirements.

ICF used in this study and any changes during the study should obtain prospective approval before use of the IRB/IEC and the sponsor.

The investigator should ensure each study patient fully understands property and objectives of the study as well as possible risks of participation in the study. The investigator or personnel designated by the investigator must obtain written informed consent document of each patient before carrying out any specific activities of the study. The investigator must keep a original copy of the signed ICF of each patient.

12.3. IRB/IEC

The investigator has the responsibility to obtain the prospective approval from IRB/IEC of study protocol, protocol amendment, ICF and other related documents (e.g., recruitment advertisement, if applicable) in advance. All correspondences with IRB/IEC should be kept in investigator's study site file.

Amendment can be implemented before obtaining IRB/IEC approval only when it is necessary to eliminate obvious direct harm to patients. In such case, the investigator should notify the IRB/IEC and the sponsor in written immediately after implementation.

12.4. Keeping confidentiality for patient

The sponsor and personnel designated by the sponsor confirm and maintain the patients' privacy right from being violated. 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 follow the requirements of ICH GCP and confirm the compliance of the protocol, 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/IEC to review patients' original medical record (source data or document), including but

not limited to any gene/genome data at testing before patients were enrolled into the investigation, laboratory test result reports, ECG reports, patients' admittance and discharge summary generated during hospitalization while participating in the investigation as well as autopsy reports.

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

12.5. Report of safety issues or conditions seriously violating the study protocol or Good Clinical Practice of ICH

If the applicable competent authority issues any prohibition or order (that is, order to suspend the clinical study) to the study or if the investigator is informed of any new information that may influence risk/benefit analysis of the study drug, it is necessary to notify the sponsor immediately.

In addition, when the investigator takes any emergent safety measures to protect patients from suffering any immediate danger and finds any behaviors seriously violating the study protocol or ICH GCP, it is necessary to notify the sponsor immediately.

13. Termination of study

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

If the investigator wishes 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 premature termination of the study

Criteria for suspension or premature termination of the study include:

1. Obtaining new information of safety or efficacy of the study drug indicates that the known risk/benefit characteristics of the compound have changed and are not suitable for patients taking part in the study.
2. Seriously violate GCP and damage the ability to realize the primary objective or threaten patients' safety.
3. The sponsor may suspend or prematurely terminate the study for reasons unrelated to the conduct of 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 and agreement or is unable to ensure normal conduct of the study, the participation of the study site in this investigation may be prematurely terminated or suspended.

13.3. Procedures for early termination or suspension of the study or participation of study site

If the sponsor chooses to terminate or suspend the study or participation of study site, the sponsor will provide a specific procedure for premature termination or suspension. Applicable study sites will comply with the procedures during study termination or suspension.

14. Publication of research results

Zai Lab (Shanghai) Co., Ltd., as the sponsor, has exclusive rights to this study. The author and manuscript 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

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16. Appendix

16.1. "RECIST v1.1-GIST-specific Criteria" response Evaluation Criteria In Solid Tumours

"RECIST v1.1-GIST-specific Criteria" include:

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

From: 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).