CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213973Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review
Clinical Microbiology/Virology

NDA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA or the other Regulatory Authorities. While the conclusions and recommendations expressed herein reflect FDA's completed review of the application, the applications submitted to the other Regulatory Authorities remain under review.

Application Type	New Molecular Entity/ Original New Drug Application
Application Number(s)	NDA 213973
Priority or Standard	Priority
Submit Date(s)	December 13, 2019
Received Date(s)	December 13, 2019
PDUFA Goal Date	August 13, 2020
Division/Office	Office of Oncologic Diseases / Division of Oncology 3
Review Completion Date	Electronic stamp date
Established Name	Ripretinib
(Proposed) Trade Name	QINLOCK
Pharmacologic Class	Tyrosine kinase inhibitor
Code name	DCC-2618
Applicant	Deciphera Pharmaceuticals
Formulation(s)	50 mg tablets
Dosing Regimen	150 mg orally once daily with or without food
Applicant Proposed Indication(s)/Population(s)	for the treatment of patients with advanced gastrointestinal stromal tumor (GIST) who have received (b) (4) (b) (4).
Recommendation on Regulatory Action	Regular approval
Recommended Indication(s)/Population(s) (if applicable)	for the treatment of patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with 3 or more kinase inhibitors, including imatinib.

Table of Contents

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Table of Tables

Table of Figures

Reviewers of Multi-Disciplinary Review and Evaluation

U.S. FDA Review Team

Regulatory Project Manager	Leah Her, M.S., P.M.P.
Pharmacology/Toxicology Reviewer(s)	Elizabeth Spehalski, Ph.D.
Pharmacology/Toxicology Team Leader(s)	Matthew Thompson, Ph.D., M.P.H.
Office of Clinical Pharmacology Reviewer(s)	Hisham Qosa, Ph.D. Youwei Bi, Ph.D. (pharmacometrics) Jillian Sun, Ph.D. (genomics)
Office of Clinical Pharmacology Team Leader(s)	Hong Zhao, Ph.D. Jiang Liu, Ph.D. (pharmacometrics) Rosane Charlab Orbach, Ph.D. (genomics)
Clinical Reviewer	Leslie Doros, M.D. (efficacy) Margaret Thompson, M.D. (safety)
Clinical Team Leader	'Lola Fashoyin-Aje, M.D., M.P.H.
Statistical Reviewer	Sirisha Mushti, Ph.D.
Statistical Team Leader	Lisa Rodriguez, Ph.D.
Associate Director for Labeling	Stacy S. Shord, Pharm.D.
Cross-Disciplinary Team Leader	'Lola Fashoyin-Aje, M.D., M.P.H.
Division Director (DHOT)	John Leighton, Ph.D., DABT
Division Director (OCP)	NAM Atiqur Rahman, Ph.D.
Division Director (OB)	Shenghui Tang, Ph.D.
Division Director (OOD)	'Lola Fashoyin-Aje, M.D., M.P.H.
Office Director (or designated signatory authority)	Marc Theoret, M.D.

Additional FDA Reviewers of Application

OPQ	Raymond Frankewich, Ph.D. (drug substance)/Ali Al Hakim, Ph.D. (Branch Chief) Tefsit Bekele, Ph.D. (drug product)/Xing Wang, Ph.D. (ATL)/Anamitro Banerjee, Ph.D. (Branch Chief) Mei Ou, Ph.D. (biopharmaceutics)/Banu Zolnik, Ph.D. (TL)
Facilities	Sridhar Thumma, Ph.D./Rakhi Shah, Ph.D. (TL)
OPDP	Robert Nguyen, Pharm.D.
DMPP	Shawna Hutchins, Ph.D./Barbara Fuller, Ph.D. (TL)
OSI	Michele Fedowitz, M.D./Karen Bleich, M.D. (TL)

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

OSE/DEPI	Richard (Scott) Swain, Ph.D., M.P.H.
OSE/DMEPA	Sarah Thomas, Pharm.D./Chi-Ming (Alice) Tu, Pharm.D. (TL)
OSE/DRISK	Mei Yean Chen, Pharm.D./Naomi Boston, Pharm.D. (TL)
QT-IRT	Girish Bende, Ph.D. / Nan Zheng, Ph.D. (TL)

OPQ=Office of Pharmaceutical Quality; OPDP=Office of Prescription Drug Promotion; DMPP=Division of Medical Policy Programs; OSI=Office of Scientific Investigations; OSE= Office of Surveillance and Epidemiology; DEPI= Division of Epidemiology; DMEPA=Division of Medication Error Prevention and Analysis; DRISK=Division of Risk Management

Health Canada Review Team

Project Management		
Post-market Reviewer		
Post-market Manager		
Label Reviewer		
Biopharmaceutics Evaluator		
Biopharmaceutics Manager		
Nonclinical Reviewer		
Clinical Pharmacology Reviewer		
Biostatistics Reviewer		
Clinical Safety Reviewer		
Cardiac Safety Reviewer		
Clinical Reviewer		
Medical Manager		
Clinical Manager		
Oncology Associate Director		
Medical Director		
Oncology Director		

Therapeutic Goods Administration (Australia) Review Team

Toxicology Reviewer		
Toxicology Team Leader		
Clinical Reviewer		
Clinical Team Leader		
Risk Management Plan Reviewer		

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AECI	adverse event of clinical importance
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC_{0-24}	area under the concentration-time curve from 0 to 24 hours
AUC_{0-t}	area under the concentration-time curve from 0 to time "t"
$AUC_{0-\infty}$	Area under the concentration-time curve to infinity
BCRP	breast cancer resistance protein
BDC	bile-duct cannulated
BICR	blinded independent review committee
BID	twice daily
BLA	biologics license application
BMI	body mass index
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
C_{max}	maximum observed concentration
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL/F	apparent systemic clearance
CMC	chemistry, manufacturing, and controls
CMQ	custom MedDRA query
COA	clinical outcome assessment
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CPK	creatine phosphokinase
CR	complete response
CRF	case report form
CRO	contract research organization

CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CYP	cytochrome P450
DCR	disease control rate
DDI	drug-drug interaction
DG	gestation day
DLT	dose-limiting toxicity
DMC	data monitoring committee
DMF	drug master file
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCTD	electronic common technical document
EOP	end of phase
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30 Item
EQ-5D-5L	EuroQol 5 Dimension 5 Level
ETASU	elements to assure safe use
λz	first-order rate constant associated with the terminal (log-linear) portion of the concentration-time curve
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FP	fluorescence polarization
GIST	gastrointestinal stromal tumor
GCP	good clinical practice
GLP	good laboratory practice
GRMP	good review management practice
HFSR	hand-foot skin reaction
HR	hazard ratio
IC_{50}	half maximal inhibitory concentration
ICH	International Conference on Harmonization
IDMC	independent data monitoring committee
IND	Investigational New Drug
INR	international normalized ratio
IRR	independent radiologic review
IRT	interactive response technology
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat

KIT	proto-oncogene receptor tyrosine kinase
LE	Long Evans
MDR1	multi-drug resistance-1
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
mPFS	median progression-free survival
mRECIST	modified Response Evaluation Criteria in Solid Tumors
MTD	maximum tolerated dose
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NCI ODWG	National Cancer Institute Organ Dysfunction Working Group
NDA	new drug application
NE	not estimable
NME	new molecular entity
NOAEL	no observed adverse effect level
NSAIDS	non steroidal anti inflammatory drugs
OCS	Office of Computational Science
OL	open-label
OPQ	Office of Pharmaceutical Quality
ORR	objective response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
$\%AUC_{extrap}$	percentage of AUC that is due to extrapolation from the last measurable concentration
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PFS	progression-free survival
P-gp	P-glycoprotein
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PR	partial response
PPES	palmar plantar erythrodysesthesia syndrome
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PT	prothrombin time
PSUR	Periodic Safety Update report
QD	once daily

QOL	quality of life
RAS-RAF	fibrosarcoma-guanosine-nucleotide-binding protein
RDW	red cell distribution width
RECIST	Response Evaluation Criteria in Solid Tumors
REMS	risk evaluation and mitigation strategy
RP2D	recommended Phase II dose
SAE	serious adverse event
SAP	statistical analysis plan
SCC	squamous cell carcinoma
SD	Sprague Dawley
SDH	succinate dehydrogenase
SEER	Surveillance, Epidemiology, and End Results Program
SGE	special government employee
SM	systemic mastocytosis
SMQ	standardized MedDRA query
SOC	standard of care
SRT	safety review team
TEAE	treatment emergent adverse event
TKI	tyrosine kinase inhibitor
$t_{1/2}$	elimination half-life
t_{max}	time to maximum observed concentration
TTP	time to tumor progression
TTR	time to response
ULN	upper limit of normal
UK	United Kingdom
US	United States
USPI	United States Prescribing Information
V_Z/F	apparent volume of distribution associated with the terminal Phase
WHO	World Health Organization
WRO	written responses only
wt	wild type

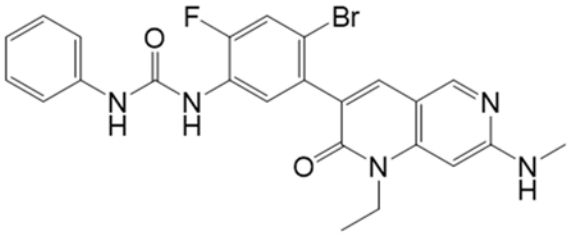
1 Executive Summary

1.1. Product Introduction

On December 13, 2019, Deciphera submitted New Drug Application (NDA) 213973 as provided for by 21 CFR 314.50, seeking regular approval of ripretinib tablets (50 mg) under Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for the following proposed indication:

> *QINLOCK is a kinase inhibitor indicated for the treatment of patients with advanced gastrointestinal stromal tumor (GIST) who have received* (b) (4) (b) (4).

Ripretinib is a tyrosine kinase inhibitor that inhibits KIT and PDGFRA kinase signaling. Ripretinib binds to both the switch pockets and the activation loop to inactivate the kinase, preventing downstream signaling and cell proliferation in wild type and primary and secondary mutations. The chemical name is 1-(4-bromo-5-[1-ethyl-7-(methylamino)-2-oxo-1,2-dihydro-1,6-naphthyridin-3-yl]-2-fluorophenyl)-3-phenylurea. The molecular formula is C24H21BrFN5O2 and the molecular weight is 510.36 g/mol. The chemical structure of ripretinib is shown below:



Ripretinib is a white to off-white crystalline solid. Ripretinib is a lipophilic, weak base compound, practically insoluble in aqueous media. Ripretinib is available as a white to off-white oval tablet for oral administration containing 50 mg of ripretinib. Each tablet contains the following inactive ingredients: hypromellose acetate succinate, microcrystalline cellulose, lactose monohydrate, crospovidone, silicon dioxide, and magnesium stearate.

The proposed dosing schedule is 150 mg administered orally once daily in continuous 28-day cycles until disease progression or unacceptable toxicity.

On December 13, 2019, the Applicant submitted a request for a review of the proposed proprietary name, QINLOCK. On March 19, 2020, FDA issued a denial letter stating that the proposed proprietary name, QINLOCK, could result in medication errors due to confusion with another product under review for approval. On March 26, 2020, the Applicant submitted a

review for the proposed proprietary name, (b) (4). Subsequently, the Division of Medication Errors Prevention and Analysis (DMEPA) concluded that based upon the proposed timelines for review and approval of the two products, should NDA 213973 be approved on or before May 18, 2020, proposed proprietary name QINLOCK would be acceptable. The Applicant resubmitted the request for the proposed proprietary name QINLOCK on April 3, 2020 and FDA issued a "Proprietary Name Request - Conditionally Acceptable" letter on April 16, 2020, stating that the Applicant's proposal for the proprietary name, QINLOCK, was found to be conditionally acceptable.

1.2. FDA Conclusions on the Substantial Evidence of Effectiveness

The recommendation for regular approval of ripretinib, according to 21 CFR, Part 314.50, Subpart B, is based primarily on efficacy and safety results of a single trial, Study DCC-2618-03-001 (also referred to as INVICTUS). Study DCC-2618-03-001 is an international, multi-center, randomized (2:1), double-blind, placebo-controlled trial that evaluated ripretinib in 129 patients with unresectable locally advanced or metastatic gastrointestinal stromal tumor (GIST) who had been previously treated with imatinib mesylate, sunitinib malate, and regorafenib. The major efficacy outcome measure is progression-free survival (PFS) assessed by blinded independent central review (BICR) using RECIST 1.1 modified for GIST (lymph nodes and bone lesions were not target lesions and a progressively growing new tumor nodule within a pre-existing tumor mass must meet specific criteria to be considered unequivocal evidence of progression). Supportive efficacy outcome measures include the overall response rate (ORR) by BICR and overall survival (OS).

INVICTUS demonstrated a statistically significant and clinically meaningful improvement in PFS for patients who received ripretinib compared to patients who received placebo. The median PFS was 6.3 months (95% confidence interval [CI]: 4.6, 6.9) for ripretinib compared to 1.0 months (95% CI: 0.9, 1.7) for placebo with a hazard ratio (HR) of 0.15 (95% CI: 0.09, 0.25; p-value of <0.0001). The ORR was 9% (95% CI: 4.2, 18) for the ripretinib group compared to 0% for the placebo group, though this difference was not statistically significant. The median OS for the ripretinib group was 15 months (95% CI: 12, 15) compared to 7 months (95% CI: 4.1, 12) for the placebo group with a HR of 0.36 (95% CI: 0.21, 0.62), though OS was not evaluated for statistical significance as a result of the sequential testing procedure for the secondary endpoints (i.e., PFS, then ORR, then OS).

There are no approved therapies for the treatment of an unselected population of patients with advanced GIST who have received prior treatment with imatinib, sunitinib, and regorafenib. This patient population with a serious and life-threatening, rare cancer, has a high unmet medical need. Progression-free survival is considered by FDA to be an acceptable endpoint to demonstrate the effectiveness of new therapeutics across many oncology indications and has

been the primary basis for approval of therapies indicated for the treatment of advanced GIST. INVICTUS provides the evidence that supports the effectiveness of ripretinib in this NDA. That a single randomized trial to support the approval of ripretinib, is acceptable in the context of the unmet medical need in the indicated population and the robustness of the efficacy results. The FDA considered the Applicant's request for approval (b) (4) (b) (4). Ultimately, the review team concluded that the supportive data submitted to support this request was insufficient. Therefore, the FDA review team recommends granting regular approval to QINLOCK (ripretinib) for the following indication:

> *QINLOCK is a kinase inhibitor indicated for the treatment of patients with advanced gastrointestinal stromal tumors (GIST) who have received prior treatment with 3 or more kinase inhibitors, including imatinib.*

1.3. FDA Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

GIST are the most common nonepithelial neoplasms affecting the gastrointestinal tract. In the United States, there are approximately 4000 to 6000 new cases diagnosed annually. The overall 5-year survival rate for GIST is 82%; however, patients with metastatic GIST have only a 52% 5-year survival (SEER data 2009 to 2015). Approximately 90% of GISTs have a mutation in KIT or platelet-derived growth factor receptor alpha (PDGFRα). The majority of KIT mutations are found in exon 11; however, mutations in exons 9, 13, or 17 have also been described. For tumors that do not have a KIT mutation, the most common mutation described is a PDGFRα D842V mutation. Tyrosine kinase inhibitors targeting KIT and PDGFR have been used successfully to treat patients with GIST, as evidenced by the previous approvals of imatinib, sunitinib, regorafenib in the 1st, 2nd, and 3rd line settings, respectively. In addition, avapritinib was approved during the review of this application for the treatment of patients with advanced GISTs that harbor a PDGFRα exon 18 mutation including PDGFRα D842V.

Ripretinib, a small molecule, switch-control tyrosine kinase inhibitor that inhibits KIT and PDGFRα mutated kinases, is recommended for approval for the treatment of patients with advanced gastrointestinal stromal tumors (GIST) who have received prior treatment with 3 or more kinase inhibitors, including imatinib. The efficacy of ripretinib was evaluated in Study DCC-2618-03-001 (INVICTUS), an international, multi-center, randomized, double-blind, placebo-controlled trial in 129 patients with unresectable, locally advanced or metastatic GIST. Eligible patients were required to have received prior treatment with at least imatinib, sunitinib, and regorafenib. Randomization was stratified by prior lines of therapy (3 versus ≥4) and Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1 or 2). Patients received ripretinib 150 mg or placebo orally once daily until disease progression or unacceptable toxicity. Tumor response assessments were performed every cycle (n=28 days) through for the first four months and then every other cycle thereafter. Patients randomized to receive placebo could be treated with ripretinib at the time of disease progression.

The major efficacy outcome was progression-free survival (PFS) based on disease assessment by blinded independent central review (BICR) using RECIST v1.1 modified for GIST (lymph nodes and bone lesions were not target lesions and a progressively growing new tumor nodule within a pre-existing tumor mass must meet specific criteria to be considered unequivocal evidence of disease progression). Additional efficacy measures included overall response rate (ORR) by BICR and overall survival (OS). Study DCC-2618-03-001 demonstrated a statistically significant and clinically meaningful improvement in PFS in patients who received ripretinib compared to patients who received placebo. The median of PFS was 6.3 months (95% confidence interval [CI]: 4.6, 6.9) in the ripretinib arm compared to 1.0 months (95% CI: 0.9, 1.7) in the placebo arm

with a hazard ratio (HR) of 0.15 (95% CI: 0.09, 0.25; p-value of <0.0001). The ORR was 9% (95% CI: 4.2, 18) for ripretinib compared to 0% for placebo, though this difference was not statistically significant. The median OS for ripretinib was 15.1 months (95% CI: 12.3, 15.1) compared to 6.6 months (95% CI: 4.1, 11.6) for placebo with a HR of 0.36 (95% CI: 0.21, 0.62), though OS was not evaluated for statistical significance as a result of the sequential testing procedure for the secondary endpoints (i.e., PFS, then ORR, then OS).

The safety of ripretinib was evaluated in patients who received at least one dose of study drug in Study DCC-2618-03-001 (ripretinib: n=85, placebo: n=43) during the double-blinded period, in a pooled safety set of 295 patients with advanced malignancies who received at least one dose of ripretinib 150 mg once daily in Studies DCC-2618-03-001 and DCC-2618-01-001, and a pooled safety set of 351 patients with advanced malignancies who received at least one dose of ripretinib in a variety of dosages in Studies DCC-2618-03-001 and DCC-2618-01-001.

Ripretinib was well tolerated with most adverse reactions reported as mild to moderate in severity. The observed toxicities are generally expected based upon the mechanism of action of ripretinib and the preclinical and clinical toxicity profile of other approved agents in the class. Among the 129 patients enrolled in Study DCC-2618-03-001, the most common adverse reactions to ripretinib (incidence ≥ 20%) are alopecia, fatigue, nausea, abdominal pain, constipation, myalgia, diarrhea, decreased appetite, palmar-plantar erythrodysesthesia syndrome (PPES), and vomiting. Clinically relevant adverse reactions occurring in ≥10% but in ≤ 20% of patients who received ripretinib include headache (19%), arthralgia (18%), blood bilirubin increased (17%), peripheral edema (17%), muscle spasms (15%), and hypertension (14%), dyspnea (13%), and hypophosphatemia and stomatitis (11% each).

Serious adverse reactions occurred in 31% of patients who received ripretinib. Serious adverse reactions reported in >2% of patients are abdominal pain, anemia, nausea, and vomiting; a fatal adverse event of hypoglycemia was reported in one patient and attributed to disease progression. Serious adverse reactions were generally manageable with dose interruptions or reduction, with 8% of patients on the ripretinib arm discontinuing treatment during the double-blinded period due to an adverse reaction. The serious risks of ripretinib observed across several clinical studies evaluating several dosages, are PPES, cutaneous squamous cell carcinoma, hypertension, cardiac dysfunction (manifesting as decreases in left ventricular ejection fraction), impaired wound healing, and embryofetal toxicity.

Overall, the toxicity profile of ripretinib is acceptable when considering the ripretinib effect on PFS in patients with refractory GIST who have a poor life expectancy and limited treatment options. The major safety risks of ripretinib are toxicities that oncologists are well-trained to manage and are acceptable for a population with a serious and life-threatening condition. As such, the FDA review team concludes that the overall benefit: risk assessment of ripretinib is favorable for the treatment of patients with advanced GIST who have received prior treatment

with 3 or more kinase inhibitors, including imatinib.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• GIST is the most common non-epithelial neoplasm affecting the gastrointestinal tract. • Annual incidence of GIST in the U.S. is 3000-6000 cases per year. • Overall 5-year survival rate for GIST is 83%; OS for metastatic GIST is 52%. • Approximately 80% of GISTs have a mutation in KIT; approximately 10% have a mutation in PDGFRα.	**Advanced or metastatic GIST is a serious and life-threatening condition.**
Current Treatment Options	• Imatinib is approved for unresectable or metastatic KIT-mutated GIST and as adjuvant treatment following resection of KIT-mutated GIST. • Sunitinib is approved for GIST after disease progression on or intolerance to imatinib. • Regorafenib is approved for locally advanced, unresectable, or metastatic GIST after previous treatment with imatinib and sunitinib. • Avapritinib is approved for unresectable or metastatic GIST harboring a PDGFRα exon 18 mutation, including PDGFRα D842V mutations.	**There is an unmet medical need for new effective treatments for patients with GIST who have received prior treatment with 3 or more kinase inhibitors, including imatinib. There are no FDA-approved therapies in the fourth line or beyond for patients who do not have a PDGFRα exon 18 mutation.**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The efficacy of ripretinib was evaluated in Study DCC-2618-03-001. The median PFS was 6.3 months (95% CI: 4.6, 6.9) for ripretinib compared to 1.0 months (95% CI: 0.9, 1.7) for placebo with a hazard ratio (HR) of 0.15 (95% CI: 0.09, 0.25; p-value of <0.0001). • ORR was 9% (95% CI: 4.2, 18) for ripretinib compared to 0% for placebo, though this difference was not statistically significant. • The median OS for ripretinib was 15.1 months (95% CI: 12.3, 15.1) compared to 6.6 months (95% CI: 4.1, 11.6) for placebo with a HR of 0.36 (95% CI: 0.21, 0.62). Note: OS was not evaluated for statistical significance as a result of the sequential testing procedure for the secondary endpoints (i.e., PFS, then ORR, then OS).	**Study DCC-2618-03-001 demonstrated a statistically significant and clinically meaningful improvement in PFS in patients who received ripretinib compared to placebo . The submitted evidence meets the statutory evidentiary standard for regular approval of ripretinib for this indication.**
Risk and Risk Management	• The most common adverse reactions (≥ 20%) included: alopecia, nausea, fatigue, abdominal pain, constipation, myalgia, diarrhea, decreased appetite, PPES, and vomiting. The majority of these ARs were Grade 1-2. • The most common laboratory abnormalities included: hypophosphatemia and hyperbilirubinemia. • Clinically relevant adverse reactions occurring in ≥10% but in ≤ 20% of patients who received ripretinib include headache (19%), arthralgia (18%), blood bilirubin increased (17%), peripheral edema (17%), muscle spasms (15%), and hypertension (14%), dyspnea (13%), and hypophosphatemia and stomatitis (11% each). • Serious adverse reactions occurred in 31% of patients who received ripretinib. Serious adverse reactions reported in >2% of patients are abdominal pain, anemia, nausea, and vomiting; a fatal adverse reaction of hypoglycemia was reported in one patient.	**Overall, ripretinib was well tolerated with most adverse reactions reported as mild to moderate in severity. The observed toxicities are generally expected based upon the mechanism of action of ripretinib and the preclinical and clinical toxicity profile of other approved agents in the class, and acceptable particularly when assessed in the context of the treatment of patients with a life-threatening condition such as advanced GIST.** **Most of the adverse reactions to ripretinib were manageable with dose modifications and supportive care as needed. The**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The serious risks of ripretinib observed across several clinical studies evaluating several dosages, are PPES, cutaneous squamous cell carcinoma, hypertension, cardiac dysfunction (manifesting as decreases in left ventricular ejection fraction), impaired wound healing, and embryofetal toxicity. • The protocol included monitoring for risks and instructions for intervention. With this in place, serious toxicities could be mitigated by dose interruption or reduction. • The proposed labeling includes warnings for concomitant use with strong CYP3A inhibitors, warnings, dose modifications, and management guidelines for serious toxicities.	**significant and potentially serious adverse reactions of ripretinib are adequately addressed in the Warnings and Precautions section and the dose modification recommendations included in product labeling.** **There were no safety concerns identified during NDA review requiring risk management beyond labeling or warranting consideration for Risk Evaluation and Mitigation Strategy (REMS).**

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

x	The patient experience data that was submitted as part of the application, include:			Section where discussed, if applicable
	□	Clinical outcome assessment (COA) data, such as		[e.g., Section 6.1 Study endpoints]
		x	Patient reported outcome (PRO)	Section 8.1.2 Study Results
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	

	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Section 2.1 Analysis of Condition]
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that was not submitted in the application, but was considered in this review.	

X

Lola A. Fashoyin-Aje, MD, MPH
Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Epidemiology and Pathology
Gastrointestinal stromal tumors (GISTs) represent the most common form of soft tissue sarcoma, a relatively rare subset of cancers arising from mesenchymal cells in the body [Aubin, 2011]. GISTs occur primarily in older patients of either sex, with annual incidences between 11 and 19.6 per million population worldwide [Corless, 2014]. Incidence estimates give a range of 3000 to 6000 new cases of GIST per year in the USA [Corless, 2008] or, based on Surveillance, Epidemiology, and End Results Program (SEER) 6.8 per million [Tran, 2005] within a population.

GIST patients have had a notable increase in prevalence due to the progress in surgical and oncological management. Estimates suggest that the prevalence is over 10-times that of the incidence, with GIST survivors now projected to be 135-155 per million per year [Søreide, 2016].

At diagnosis, prognosis can vary based on tumor size, mitotic rate, location, and mutation status. In general, small tumors of less than 2 cm are considered low risk for metastasis whereas larger tumors carry more risk, particularly if they are of a higher mitotic rate. Additionally, GIST in the stomach is typically of a lower risk compared to those found in the intestines. Mutation status has some correlation to risk but is not commonly included in prognosis classification tools [ESMO, 2018].

Molecular subtypes of GIST
GISTs are primarily characterized by gain-of-function mutations in proto-oncogene proteins, proto-oncogene receptor tyrosine kinase (KIT) or platelet-derived growth factor receptor alpha (PDGFRA). The majority of GISTs harbor primary driver mutations in the KIT gene (80-85%) affecting the juxtamembrane, extracellular, or catalytic kinase domains, and consist of in-frame deletions or insertions, or missense mutations [Emile, 2011]. In GIST patients at presentation, mutations in the KIT gene are usually found in exon 9 or 11. Primary mutations in exon 11 disrupt the autoinhibited form of the kinase, and those in exon 9 increase receptor dimerization. Primary mutations in PDGFRA are less frequent (5-10%) in GIST patients and are mostly found in the catalytic domain of the kinase, while some are found in the juxtamembrane region [Kee, 2012; Demetri, 2007].

Such mutations, regardless of location, act to disrupt the autoinhibited forms of KIT and PDGFRA kinases and cause constitutive (ligand-independent) activation of downstream signaling, leading to uncontrolled cell growth and cell transformation, ultimately tumor growth and metastasis [Rubin, 2001; Blay, 2010].

A small percentage of GISTs are classified as KIT/PDGFRA wild type (10-15%) due to the absence of driver mutations in either KIT or PDGFRA [Kee, 2012; Demetri, 2007]. Recent advances have revealed that KIT/PDGFRA wild type GISTs are comprised of molecularly heterogenous subgroups, which has led to further stratification [Nannini, 2013]. The largest subgroup of wild type GIST is characterized by deficiencies in the succinate dehydrogenase (SDH) complex caused by mutation or epigenetic silencing [Boikos, 2016], while GISTs with a functioning SDH pathway have been further categorized by the presence of mutations in the rapidly accelerated fibrosarcoma-guanosine-nucleotide-binding protein (RAS-RAF) signaling pathway, most frequently BRAF, RAS, or NF1. Together, GISTs with SDH deficiencies or RAS-RAF pathway deregulation account for half of all KIT/PDGFRA wild type GISTs. The remaining half of KIT/PDGFRA wild type GIST are thus considered quadruple wild type GIST or KIT/PDGFRA/RAS/SDH wild type GIST [Pantaleo, 2015] due to the absence of mutations in any of the genes listed.

The Regulatory Authorities' Assessment:

The Regulatory Authorities generally agree with the Applicant's assessment of GIST.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

Surgical resection is the only potentially curative treatment for patients with GIST; however, there is a 50% recurrence [Kee, 2012]. On average, the 5-year survival rate is about 54% and the disease-free survival rate is 45%; however, disease-free survival rates are lower for patients in high-risk categories [Maleddu, 2011]. For metastatic or unresectable GIST, which is present in about half of patients at diagnosis, radiotherapy and traditional chemotherapy are not effective [Aubin, 2011; Eisenberg, 2011]. There are three Food and Drug Administration (FDA) approved tyrosine kinase inhibitors that are indicated to treat patients with this disease: imatinib, sunitinib, and regorafenib. The results from the registration studies for these therapies are provided in Table 1.

Table 1: Summary of GIST Indicated Therapies Approved in the United States

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Tyrosine Kinase Inhibitor Therapies					
Gleevec (imatinib) [GLEEVEC® US Package Insert 2019]	Treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST)	2002	400 mg/day	400 vs. 800 mg unresectable GIST Median PFS: 18.9 (95% CI: 17.4, 21.2) vs. 23.2 months (95% CI: 20.8, 24.9) Median OS: 49.0 (95% CI: 45.3, 60.0) vs. 48.7 (95% CI: 45.3, 51.6) months	Edema Cytopenia Severe congestive heart failure Severe or fatal hepatotoxicity Hemorrhage Gastrointestinal perforations Cardiogenic shock/left ventricular dysfunction Bullous dermatologic reactions Hypothyroidism Fetal harm Growth retardation Tumor lysis syndrome Renal toxicity
Sutent (sunitinib) [SUTENT® US Package Insert 2019]	The treatment of gastrointestinal stromal tumor (GIST) after disease progression on or intolerance to imatinib	2006	50 mg/day x 4 weeks followed by 2 weeks off treatment	vs. placebo Median TTP: 27.3 (95% CI: 16.0, 32.1) vs. 6.4 weeks (95% CI: 4.4, 10.0) HR= 0.33 (95% CI: 0.23, 0.47) p < 0.0001	Severe or fatal hepatotoxicity Cardiovascular events Prolonged QT intervals and Torsade de Pointes Hypertension Hemorrhagic events Cases of Tumor Lysis Syndrome (TLS) Thrombotic microangiopathy

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
				Median PFS: 24.1 (95% CI: 11.1, 28.3) vs. 6 weeks (95% CI: 4.4, 9.9 HR= 0.33 (95% CI: 0.23, 0.47) p < 0.0001 Median OS[1]: 72.7 vs. 64.9 weeks HR = 0.88 (95% CI: 0.679, 1.129)	Proteinuria Necrotizing fasciitis Thyroid dysfunction Hypoglycemia Osteonecrosis Wound Healing Embryo-Fetal Toxicity
Stivarga (regorafenib) [STIVARGA® US Package Insert 2019]	Treatment of patients with locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib and sunitinib	2013	160 mg/day x 21 days of each 28 day cycle	vs. placebo Median PFS: 4.8 (95% CI: 3.9. 5.7) vs. 0.9 months (95% CI: 0.9, 1.1) HR= 0.27 (95% CI: 0.19, 0.39) p < 0.0001 Median OS[2]: 17.4 vs. 17.4 months HR= 0.91 (95% CI: 0.65, 1.27)	Severe or fatal Hepatotoxicity Infections Hemorrhage Gastrointestinal perforation or fistula Dermatological toxicity Hypertension Cardiac ischemia and infarction Reversible Posterior Leukoencephalopathy Syndrome (RPLS) Wound healing complications Embryofetal toxicity

Abbreviations: CI = confidence interval; PFS = progression-free survival; OS = overall survival.
[1]OS based on post interim analysis data cutoff value.
[2]OS based on post final analysis data cutoff value.

Imatinib was the first KIT therapy approved (2002) and changed the prognosis for many patients with metastatic or unresectable GIST. Imatinib therapy is usually not curative, as complete response rates of only ~5% and an overall response rate of 68% were seen in clinical trials [Blanke, 2008]. More than 80% of GIST patients will receive clinical benefit from imatinib therapy, but as development of imatinib-resistance is essentially inevitable, more than half will develop progressive disease by 2 years [Kee, 2012]. Progression is largely due to secondary mutations in the KIT kinase domain that cause resistance to imatinib [Care, 2003].

Patients with GIST with KIT exon 11 mutations that are CD117 (ie, KIT protein) immunohistochemical positive will have the best response to imatinib and are started at 400 mg daily dose. High risk patients may be treated with imatinib for 3 years or longer following surgery as adjuvant therapy has shown clinical benefit. Rapid disease progression has been seen when discontinuing KIT therapies in high risk tumor types. If disease progression occurs, the dose may be increased to 800 mg but dose escalation response for progression-free survival (PFS) is short-lived with a median time to progression of about 11 weeks [Kee, 2012; Demetri, 2007]. Little to no response is seen for other KIT mutations, particularly those that affect the adenosine triphosphate (ATP)-binding pocket or activation loop of the kinase domain [Kee, 2012; Demetri, 2007]. Additionally, imatinib is not routinely provided to patients with KIT/PDGFRA wild type GIST as it does not appear to offer much benefit [Heinrich, 2003; Casali, 2018].

There are three types of disease progression due to resistance seen with imatinib-therapy. (1) Primary resistance occurs in about 10-15% of patients that do not respond to therapy or achieve disease stabilization within the first 3-6 months of treatment; (2) Acquired secondary resistance occurs in about 2 years and usually results from secondary KIT mutations. The frequency of disease progression due to secondary mutations when the primary tumor was mutated in KIT exon 9 or 11 is over 50% [Meleddu, 2011]. The secondary mutations generally seen for primary KIT exon 11 tumors are in exon 13, 14 (ATP binding pocket) or 17 (kinase domain) [Kee, 2012]; (3) Disease progression due to pharmacokinetic resistance occurs in up to 30% of patients from inadequate drug exposure for a variety of reasons such as inadequate dose used for patients with an exon 9 mutation, poor patient compliance or concomitant drug interactions [Kee, 2012].

In 2003, activating mutations in the PDGFRA gene were identified as an alternative driver of GIST growth in patients lacking KIT mutations. The most common PDGFRA mutation identified in patients with GIST is the D842V mutation in exon 18, which confers resistance to imatinib [Yoo 2016a; Cassier, 2012]. Recent clinical studies suggest that treating patients with PDGFRA mutations not involving D842V with imatinib may provide some clinical benefit. This population of patients is small and thus information regarding secondary mutations in PDGFRA driven GIST is limited due to the lack of effective therapy targeting the D842V mutation.

Sunitinib was approved in 2006 as a second line therapy for GIST patients who had disease progression on or intolerance to imatinib. Sunitinib has greater activity against KIT exon 9 mutations compared to imatinib and less activity against KIT exon 11 in comparison [Kee, 2012; Meleddu, 2011; Heinrich, 2008; Garcia-Montero, 2006]. Additionally, sunitinib shows activity against KIT exon 13 and 14 mutations and KIT/PDGFRA wildtype but only half the patients show benefit and median progression-free survival (mPFS) is approximately 5.5 months [Kee, 2012]. Sunitinib is not effective against KIT exon 17 and 18, and PDGFRA exon 18 activation loop mutations.

Sunitinib is active in some imatinib-resistant patients with certain secondary mutations, yet most patients again relapse within six months to one year due to additional or alternative secondary mutations in KIT, or due to multiple different KIT mutations occurring in different areas of the tumor [Corless, 2011]. In addition, some imatinib resistant patients have primary resistance to sunitinib due to the specific secondary mutation(s) that arise during imatinib treatment [Demetri, 2013].

Regorafenib was approved in 2013 as a third line therapy for adult patients with metastatic and/or unresectable GIST who have had disease progression on or intolerance to imatinib and sunitinib treatment [George, 2012; Demetri, 2013]. Regorafenib is active in some imatinib and/or sunitinib resistant patients with certain secondary mutations in KIT (exon 11 and exon 9) however; responses are brief, and relapse occurs within six months for a majority of patients [Demetri, 2013]. Several secondary KIT mutations that do not respond to any FDA approved therapies are enriched in resistant tumors during treatment, including those mutations found in exon 13 and exon 17.

In addition to being active against KIT exon 11 mutations, regorafenib is the only approved therapy with activity against a subset of KIT exon 17 mutations and for patients who respond, PFS is approximately 5 months. KIT/PDGFRA wild type patients that respond to regorafenib experience a mPFS of 1.6 months [Ben-Ami, 2016]. Some patients present with mutations in KIT that are not effectively treated by regorafenib, and additionally, other or multiple secondary mutations arise and cause resistance to therapy [Care, 2003].

For patients who have progressed on the approved agents, progression of KIT driven tumors is primarily driven by further heterogenous KIT resistance mutations. There are limited data to support that rechallenge with prior failed treatment options. A Korean, single-center, randomized, placebo-controlled study (ie, 'RIGHT Trial') demonstrated that a rechallenge with imatinib provides a small benefit (mPFS of 1.8 months) to some patients compared to placebo (mPFS of 0.9 months) [Kang, 2013]. The study did not show any accompanied symptom palliation based on a health related quality of life analyses using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30 item (EORTC

QLQ-C30) [Yoo, 2016]. The RIGHT Trial excluded patients who had only a limited benefit from initial treatment with imatinib (PFS of ≤6 months). A rechallenge with imatinib is not an approved treatment option anywhere in the world. Once patients have received imatinib, sunitinib, and regorafenib, there are no other approved treatment options for patients with advanced or unresectable GIST.

The Regulatory Authorities' Assessment:

The Regulatory Authorities generally agree with the Applicant's assessment of therapies for the treatment of GIST in the US.

Although the Applicant stated that the average the 5-year survival rate for patients with GIST is approximately 54% based on an article by Maleddu et al, survival rates have varied in the setting of changes in the treatment landscape for GIST, with more available treatment options. This reviewer notes SEER data from 2009 to 2015 which indicate an overall 5-year survival of 83% in patients with GIST, with a 52% 5-year survival rate for those patients with metastatic disease.

In addition to the three FDA-approved therapies described, avapritinib was approved on January 9, 2020 for the treatment of for unresectable or metastatic GIST harboring a PDGFRα exon 18 (non-D842V) mutation based on an ORR of 84% (95% CI: 63, 93), and tumors harboring a PDGFRα D842V mutation based on an ORR of 89% (95% CI: 75, 97).

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Ripretinib is not currently approved in the United States (US) or any other country.

The Regulatory Authorities' Assessment:

The Regulatory Authorities acknowledge the Applicant's statement above.

3.2. Summary of Presubmission/Submission Regulatory Activity The Applicant's Position:

The Investigational New Drug (IND) application was opened for IND 125279 on August 11, 2015. A summary of key regulatory milestones related to the IND are provided in Table 2.

Table 2: IND 125279 Key Regulatory Milestones

Type of Meeting	Date	Summary
Type B, EOP1	May 26, 2017	Discussion of the proposed nonclinical, clinical and clinical pharmacology development plans, including the design of the proposed pivotal Phase 3 Study DCC-2618-03-001 in order to support the registration of ripretinib for the treatment of patients with advanced GIST who have received prior treatment with imatinib, sunitinib, and regorafenib
DCC-2618-03-001 (INVICTUS) Protocol Submission	August 17, 2017	Initial protocol submission of registration-enabling study, Protocol DCC-2618-03-001 INVICTUS, entitled "A Phase 3, Interventional, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of DCC-2618 In Patients with Advanced c-KIT/PDGFRA Gastrointestinal Stromal Tumors who have Received Prior Treatment with Imatinib, Sunitinib, and/or Regorafenib.
	November 7, 2017	*Amendment 1*
	March 1, 2018	*Amendment 2*
	March 22, 2018	*Amendment 3*
	August 27, 2018	*Amendment 4*

Type of Meeting	Date	Summary
	October 30, 2018	*Amendment 5*
Type B, Pre-Phase 3 Meeting	March 21, 2018	Discussion of the proposed Phase 3, Study DCC-2618-03-002 in order to support the registration of the second indication of ripretinib (b) (4) (b) (4) for which a supplemental NDA will be submitted to the FDA.
Type C, EOP2 - CMC	November 27, 2018	Discuss CMC development program for ripretinib and registration plans for the first indication of ripretinib.
Type C, WRO	February 13, 2019	Discuss NDA-related topics that are considered procedural and administrative in nature to support the planned marketing application for the first indication.
FDA Advice Letter	March 14, 2019	FDA additional information regarding Integrated Summary of Efficacy
Fast Track Designation	June 21, 2019	Fast Track Designation was granted for the treatment of patients with advance GIST who have received prior treatment with imatinib, sunitinib, and regorafenib, to demonstrate clinically meaningful and statistically robust improvement in PFS compared to placebo.
Statistical Analysis Plan (SAP) Submission	August 8, 2019	Submission of SAP for INVICTUS (DCC-2618-03-001)
Type B, Pre-NDA	October 9, 2019	Discuss content and format of the planned submission of a New Drug Application (NDA) for ripretinib for the treatment of patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with imatinib, sunitinib, and regorafenib.
Breakthrough Designation	October 10, 2019	Breakthrough Therapy Designation was granted for the treatment of patients with advanced GIST who have received prior treatment with imatinib, sunitinib, and regorafenib.
Proprietary Name Request	November 1, 2019	Submission of proprietary name request for ripretinib

Abbreviations: EOP = end of phase; NDA = new drug application; CMC = chemistry, manufacturing and controls; WRO = written responses only.

The FDA's Assessment:

The FDA generally agrees with the Applicant's assessment of regulatory interactions relevant to this NDA. Additionally, FDA notes that during the EOP1 meeting on May 26, 2017, FDA requested that the Applicant revise the study population in the DCC 2618-03-001 trial to include patients who had received all three FDA-approved therapies as prior therapies, and to

allow inclusion of patients who had received 4 or more prior therapies. At the time of submission of the meeting package, there was insufficient information to support a recommended dose of 150 mg daily. The Sponsor stated that in addition to pharmacokinetic data, clinical data on more than 50 patients dosed at 150 mg once daily would be available prior to study initiation, to justify the proposed recommended dose.

FDA also notes that during the pre-NDA meeting held between Deciphera and the Division of Oncology Products 2 (DOP2) on October 9, 2019, the Sponsor confirmed intent to participate in Real-Time Oncology Review (RTOR) and the Assessment Aid (AAid) pilot programs for the NDA. The RTOR submission plan for the planned ripretinib NDA was also discussed; on October 24, 2019, Deciphera submitted a revised submission plan.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Overall, the assessment of the clinical data did not raise any concerns regarding whether the studies included in this NDA submission were conducted according to good clinical practice. The FDA clinical team requested inspections at three clinical investigator study sites: Dr. Rodolfo Bordoni (#104), Dr. Scott Okuno (#116), and Dr. Cesar Serrano (#601). These sites were selected for clinical inspection because they enrolled the largest number of study participants.

The inspections of the three investigator sites and the Sponsor revealed no significant objectionable findings related to the data integrity or human subject protection in the conduct of Study DCC-2618-03-001. There was no evidence of underreporting of significant or unexpected adverse events. Based on these inspection results, the data generated by the inspected clinical sites, submitted by the Applicant, appears acceptable in support of this NDA. In addition to the inspection of the study sites, Deciphera Pharmaceuticals, LLC. was also inspected and the compliance classification was NAI.

4.2. Product Quality

According to the product quality review, complete chemistry, manufacturing, and controls (CMC) information was included in the NDA submission; the FDA reviewers found the information to adequate. All the facilities were deemed approvable based on acceptable compliance history and pre-approval inspections.

The CMC review team determined that the Applicant provided adequate information in the NDA submission to describe the relevant properties of ripretinib drug substance and drug product. The drug product (ripretinib tablets 50 mg) is an immediate-release tablet for oral administration with no coating. During the drug product manufacturing process, (b) (4) (b) (4)

The Office of Pharmaceutical Quality (OPQ) recommends approval of NDA 213973 for ripretinib 50 mg tablet. OPQ grants an 18-month expiration period to the drug product when stored in the original container at 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C to 30°C (59°F to 86°F). Refer also to product labelling for USP controlled room temperature. In addition, OPQ grants a (b) (4) month re-test period for the drug substance when stored (b) (4) (b) (4).

Refer to the full product quality review by the OPQ review team (Raymond Frankewich, Ph.D. and Ali Al Hakim, Ph.D. (drug substance), Tefsit Bekele, Ph.D., Xing Wang, Ph.D., and Anamitro Banerjee, Ph.D. (drug product), and, Mei Ou, Ph.D. and Banu Zolnik, Ph.D. (biopharmaceutics).

4.3. Clinical Microbiology

This section is not applicable.

4.4. Devices and Companion Diagnostic Issues

This is section is not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Ripretinib is a small molecule tyrosine kinase inhibitor of the KIT proto-oncogene receptor tyrosine kinase (KIT) and the platelet derived growth factor receptor α (PDGFRα). The established pharmacologic class is kinase inhibitor.

In an in vitro assay, ripretinib inhibited the kinase activity of KIT and PDGFRα with IC_{50} values of 3 and 3.4 nM, respectively. Ripretinib also inhibited phosphorylation of the kinases KDR, PDGFRβ, TIE2, and FMS with IC_{50} values of 3.4, 9, 5.4, and 123 nM, respectively. In secondary pharmacology in vitro kinase inhibition assays, ripretinib inhibited numerous kinases within 10-fold of the KIT kinase IC_{50} value of 3 nM including ARAF, BRAF, CRAF DDR2, EPHA2/4/5, EPHB1/2, FLT3, FMS, FRK, HIPK4, KDR, LCK, LYN, p38α, PDGFRα, PDGFRβ, RAF1, RET, TAOK2/TAO1, and ZAK. In human gastrointestinal tumor cells, ripretinib induced inhibition of cell proliferation with IC_{50} values as low as 3.2 nM, showing selectivity towards cell lines dependent on KIT and PDGFRα activation as compared to cell lines harboring mutations in BRAF, KRAS, and NRAS. In vivo, the anti-tumor activity of ripretinib was evaluated in mice implanted with exon 11 deleted KIT mutant GIST T1 human gastric carcinoma cells and H1703 PDGFRA-amplified human non-small cell lung cancer cells. In these studies, administration of ripretinib resulted in tumor growth inhibition compared to vehicle controls and complete tumor regression in a subset of animals.

The Applicant conducted stand-alone GLP-compliant safety pharmacology studies in rats and dogs to assess the effects of ripretinib on the central nervous system, respiratory function, and the cardiovascular system. There were no ripretinib-related adverse effects on the central nervous system. A single dose of ripretinib in beagle dogs resulted in increases in heart rate of up to 129% with secondary decreases in QT and PR intervals, as well as increases in diastolic and mean arterial pressure starting at 7 mg/kg; however, ripretinib did not appear to influence QTc intervals. Dose-dependent decreases in tidal volume were also observed in rats following a single dose of ripretinib, but these decreases were mild and reversible after a recovery period.

Following a single oral dose of radiolabeled ripretinib, fecal elimination was the major elimination pathway in rats. Hepatobiliary excretion was also a significant route of elimination, with approximately 13% of the dose recovered in bile. Renal excretion was a minor route of elimination, with approximately 1% to 4% of the dose recovered in urine. No human-specific or human-disproportionate metabolites of ripretinib were observed. In humans, as well as in the mouse, rat, dog, and monkey, the most abundant metabolite of ripretinib (DP-5439) is the result of its N-demethylation. DP-5439 is an active metabolite that inhibits KIT and PDGFRα with IC_{50}s of 2.9 and 3.1 nM, respectively. DP-5439 was not mutagenic in the in vitro bacterial

reverse mutation (Ames) test or clastogenic in either the in vitro chromosomal aberrations assay in isolated human lymphocytes or the in vivo micronucleus and comet assays. The remaining metabolites C1, C2, C3, C4, and C5 (two oxidation products and their sulfate conjugates) ranged from <1% to 5%.

To assess its safety, the Applicant conducted GLP-compliant toxicology studies of daily oral administration of ripretinib up to 13 weeks in Sprague Dawley rats and Beagle dogs. The major target organ of toxicity in both species was the skin; in the rat, the teeth, lung, and male reproductive tract were additional target organs.

In the 13-week study in rats, treatment with ripretinib at 300 mg/kg daily (approximately equal to the clinical exposure at the recommended human dose of 150 mg daily based on an estimated combined steady state AUC_{0-12} of ripretinib and major metabolite DP-5439), resulted in the death of one main study animal and two toxicokinetic study animals due to treatment-related skin lesions. In the skin, hyperplasia/hyperkeratosis of the epidermis was observed at doses ≥30 mg/kg (approximately 0.5 times the clinical exposure at 150 mg), while clinical observations of discolored and/or scaly skin, piloerection and rough hair coat, and sores and scabs, and alopecia or thinning hair coat were reported at doses of 300 mg/kg. These observations were accompanied by microscopic findings of serocellular crust, squamous cell hyperplasia, and inflammation. Hematological indications of this inflammatory response were observed and included minimal to mild increases in white blood cell, neutrophil, and platelet counts. In the lung, hypertrophy/hyperplasia of the blood vessels as well as hypertrophy/hyperplasia and vacuolation of the bronchiolar epithelium were observed at doses ≥30 mg/kg. Ripretinib-related minimal to marked incisor degeneration was observed in female rats at doses ≥30 mg/kg and males at doses of 300 mg/kg and correlated with clinical observations of clear oral discharge and missing and discolored teeth. In the male reproductive compartment, ripretinib-related testicular degeneration/atrophy and cellular debris of the epididymis was observed at doses ≥30 mg/kg. Severe degeneration of the Brunner's glands was observed in two female rats dosed at 300 mg/kg and increased osteoblastic surface and decreased trabeculae of the femur occurred in animals administered ≥30 mg/kg. Decreased body weight and body weight gain were observed for all ripretinib treated animals. Decreased food consumption was observed for males administered ≥ 100 mg/kg. With the exception of findings in the testes, epididymis, and missing teeth, all findings in rats were partially to fully reversible within the recovery period.

In the 13-week dog study, one animal dosed with ripretinib at 10 mg/kg daily (approximately 0.2 times the estimated clinical exposure at 150 mg daily) was euthanized in moribund condition due to weight loss, poor body condition, inflamed skin around the eyes, and redness and swelling of the muzzle and paws. Although it is not clear if the test article was the direct cause of death, because the animal was weakened from poor acclimation, the condition of the

dog was likely exacerbated by ripretinib administration. In the skin, minimal to moderate hyperplasia/hyperkeratosis, minimal to slight mixed cell inflammation, and minimal to moderate erosion/ulcer and crust were present in animals administered ≥ 5 mg/kg (approximately 0.1 times the clinical exposure at 150 mg). Clinically, these animals were observed to have broken, scaly, or discolored skin with scabs and sores, and a thinning hair coat. Dogs dosed at 10 mg/kg were administered antibiotics and non-steroidal anti-inflammatory drugs starting from Week 6 until necropsy due to the severity of the skin lesions. Other clinical observations included decreased body weight and body weight gain for all ripretinib treated animals, and an increase in body temperature for animals dosed at ≥ 5 mg/kg. All findings in dogs were partially to fully reversible within the recovery period with the exception of discolored skin.

Ripretinib was not mutagenic in the in vitro bacterial reverse mutation (Ames) test or clastogenic in either the in vitro chromosomal aberrations assay in isolated human lymphocytes or the in vivo micronucleus and comet assays in rats.

To assess ripretinib effects on embryo-fetal development, the Applicant conducted studies in rats and rabbits. Female rats were administered ripretinib once daily from gestation day (GD) 6 through 18 at doses of 1, 5, and 20 mg/kg. At the dose of 20 mg/kg daily (approximately 0.4 times the estimated clinical exposure at 150 mg), fetal malformations associated with the cardiovascular and skeletal systems were observed. These malformations included absent digits, mal-positioned pinna, small head, malformed ribs and vertebrae, interrupted aortic arch, retroesophageal aortic arch, and absent innominate artery. Reduced maternal weight gain occurred at doses ≥5 mg/kg (approximately 0.02 times the estimated clinical exposure at 150 mg). In pregnant rabbits, early embryonic death occurred in all animals dosed with ripretinib at 150 mg/kg daily from GD 7 through 19 (approximately 3.5 times the estimated clinical exposure at 150 mg). In animals dosed at 40 mg/kg (approximately 2.1 times the estimated clinical exposure at 150 mg), an increase in incidence of post-implantation loss and a reduction in fetal body weight were observed.

Based on the data from the embryo-fetal development studies and the drug's mechanism of action, the prescribing information (PI) includes a warning for embryo-fetal toxicity. The PI also advises females of reproductive potential to use contraception for at least one week after the last dose of QINLOCK and males with female partners of reproductive potential to use contraception for at least one week after the final dose, consistent with currently recommended timeframes for contraception for non-genotoxic drugs that are teratogenic. No studies were recommended nor conducted to investigate the effect of ripretinib on fertility or the presence of ripretinib in breast milk. Because many drugs are secreted in milk, the PI includes a warning not to breastfeed during treatment with QINLOCK for one week after the final dose, based on the half-life of the drug.

There are no outstanding issues from a pharmacology/toxicology perspective that would preclude the approval of QINLOCK.

5.2. Referenced NDAs, BLAs, DMFs

There are no referenced new drug applications (NDAs), biologic license applications (BLAs), or drug master files (DMFs) related to nonclinical pharmacology or toxicology for ripretinib.

The Regulatory Authorities' Assessment:

The Regulatory Authorities agree.

5.3. Pharmacology

Primary pharmacology

A. In Vitro Studies

The Applicant utilized a coupled spectrophotometric assay to assess the in vitro activity of ripretinib and its metabolite DP-5439 against wild type KIT, PDGFRα, and PDGFRβ recombinant kinases as well as oncogenic KIT and PDGFRα variants (Study DCC-2618-02-0001, DC-2618-02-0003). This assay indirectly measures kinase activity by the measurement of kinase production of ADP. Pyruvate kinase subsequently converts the kinase product ADP to ATP. The product of this reaction, pyruvate, is reduced by lactate dehydrogenase, resulting in a decrease in NADH absorbance readout. In the presence of 1 mM ATP, ripretinib and its metabolite DP-5439 demonstrated in vitro inhibitory activity against wild type KIT, PDGFRα, PDGFRβ and oncogenic KIT and PDGFRα variants with IC_{50} values as low as 3 nM.

In vitro inhibition by ripretinib

Kinase	Variant	Average IC_{50} (nM)	
		Ripretinib	DP-5439
KIT	Wild type	3	2.9
	D816V	25	19
	D816H	18	15
	T670I	9.2	3.4
	V654A	11	11
PDGFRA	Wild type	3.4	3.1
	D842V	36	42
PDGFRB	Wild type	4	5

Source: Data summarized from Study DCC-2618-02-0001, DCC-2618-02-0003

Using a KINOMEscan™ assay, the Applicant confirmed binding of ripretinib and DP-5439 to KIT,

PDGFRα, and oncogenic KIT variants. KINOMEscan™ is a competition binding assay that measures the ability of a compound to compete with a DNA-tagged kinase for an immobilized, active-site directed ligand using quantitative PCR (Study DCC-2618-02-0002). Ripretinib and DP-5439 bound to wild type KIT, KIT mutants, and PDGFRα with K_ds as low as ~5 nM but did not bind the autoinhibited form of wild type KIT.

Binding affinity of ripretinib (DCC-2618) for KIT, KIT mutants, and PDGFRα

	wild type KIT	KIT V559D Exon 11	KIT V559D/ V654A Exons 11/13	KIT V559D/ T670I Exons 11/14	KIT L576P Exon 11	KIT D816H Exon 17	KIT D816V Exon 17	KIT A829P Exon 18	KIT auto-inhibited	wild type PDGFRA
Compound	**K_d (nM)**									
DCC-2618	7.8	8.8	33	25	24	53	13	11	1200	21
DP-5439	4.8	14	57	31	27	37	18	33	960	11

Source: Applicant Figure reproduced from Study DCC-2618-02-0002

The Applicant assessed the ability of ripretinib to inhibit the phosphorylation of wild-type KIT and KIT family kinases (Study DCC-2618-02-0015, DCC-2618-02-0013). Briefly, cells expressing the kinase target of interest were incubated with ripretinib, DP-5439, or dimethyl sufloxide (DMSO) control for 4 hours. Cells were stimulated with the appropriate growth factor ligand for 5 to 15 minutes and were lysed. Levels of phosphorylation were measured using sandwich ELISA assays, except for wild-type KIT phosphorylation, which was assessed by western blot. Ripretinib inhibited the phosphorylation of KIT family kinases with IC_{50} values as low as 3.4 nM.

Inhibition of KIT and KIT family kinase phosphorylation by ripretinib

Tyrosine Kinase	Average IC_{50} (nM)	
	Ripretinib	DP-5439
KIT	36	-
KDR	3.4	0.6
PDGFRα	9.3	3.3
PDGFRβ	9	2.9
FMS	123	-

Source: Data summarized from Study DCC-2618-02-0015, DCC-2618-02-0013

The Applicant also evaluated the ability of ripretinib to inhibit the phosphorylation of a panel of KIT mutations identified in tumors that developed resistance to imatinib and sunitinib (Study DCC-2618-02-0012). In this assay, clinically relevant imatinib resistant c-KIT mutant genes were constructed by site-directed mutagenesis and transfected into Chinese hamster ovary (CHO-K1) cells. Cells were incubated with ripretinib, DP-5439, or DMSO for 4 hours. Cells were lysed and phosphorylation of KIT was detected using a human phospho-c-KIT ELISA. Ripretinib inhibited KIT mutants with IC_{50} values ranging from 1.4 to 221 nM.

Inhibition of phosphorylation of KIT by ripretinib for clinically relevant primary and secondary KIT mutations

Mutant c-KIT construct	Average IC_{50} (nM)	
	Ripretinib	DP-5439
A502/Y503 duplication	44	257
A502/Y503 duplication/V654A	140	710
A502/Y503 duplication/N655S	63	60
A502/Y503 duplication/N680K	47	129
A502/Y503 duplication/D816G	20	48
A502/Y503 duplication/D816H	14	102
A502/Y503 duplication/D820E	31	99
A502/Y503 duplication/D820G	16	54
A502/Y503 duplication/D820N	12	111
A502/Y503 duplication/D820V	7.9	57
A502/Y503 duplication/D820Y	14	116
A502/Y503 duplication/N822H	25	169
A502/Y503 duplication/N822K	17	47
A502/Y503 duplication/N822T	13	72
A502/Y503 duplication/N822Y	22	44
A502/Y503 duplication/S840N	38	343
W557/K558 deletion/V559C/T670I	183	121
W557/K558 deletion/V559C/D820A	7.2	26
W557/K558 deletion/V559C/D820Y	5.9	21
W557/K558 deletion/V559C/N822K	1.4	11
W557/K558 deletion/V559C/Y823D	5.3	31
V560D	4	45
V560D/V654A	189	191
V560D/T670I	221	88
V560D/N822K	21	49
V560D/Y823D	23	51
V560D/A829P	2.3	18

-Mutant c-KIT constructs have a primary mutation in either exon 9 (A502/Y503 duplication) or exon 11 (W557/K558 deletion/V559C or V560D) with secondary mutations in exon 13, 14, or 17.

Source: Data summarized from Study DCC-2618-02-0012

In a similar study, ripretinib inhibited phosphorylation of D842V PDGFRα in CHO cells with an IC_{50} of 72 nM (Study DCC-2618-02-0016) and human TIE2 with an IC_{50} of 5.4 nM (Study DCC-2618-02-0027). D842V PDGFRα is a loop mutation that has been shown to drive subsets of GIST and to exhibit resistance to imatinib, sunitinib, and regorafenib.

The Applicant assessed the ability of ripretinib to inhibit the proliferation of tumor cell lines, including gastrointestinal stromal tumor (GIST) cell lines dependent on KIT activation (Study DCC-2618-02-0005, DCC-2618-02-0010). Cells were incubated with ripretinib, DP-5439, or DMSO control for 72 or 120 hours. Cell proliferation was measured by fluorescence intensity via the addition of resazurin 2 to 6 hours before the end of the assay. Resazurin is reduced to the fluorescent product resorufin in actively growing cells. Ripretinib selectively inhibited the

proliferation of KIT activation dependent cell lines with IC_{50} values as low as 3.2 nM, with weaker activity towards cell lines driven by mutations in other kinases.

Inhibition of tumor cell proliferation by ripretinib

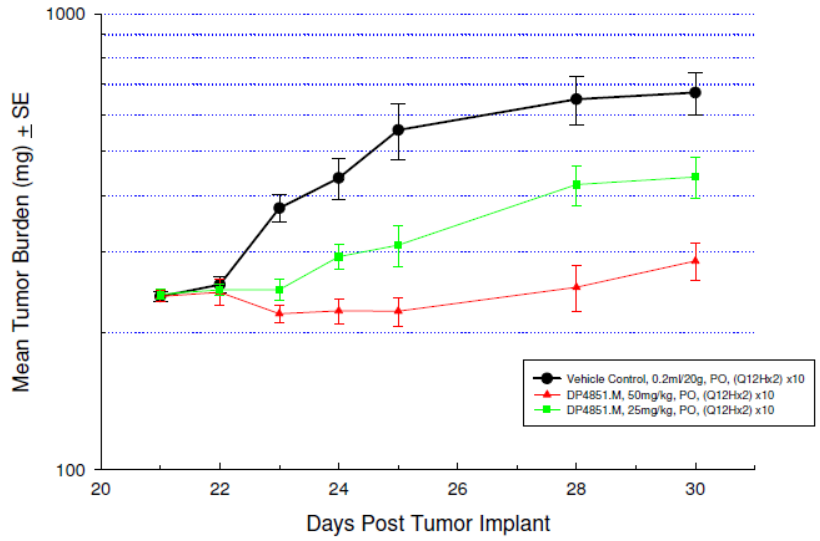
Cell line	Cancer type	Description	Average IC_{50} (nM)	
			Ripretinib	DP-5439
GIST 430	GIST	Primary in-frame deletion in exon 11 in KIT, V654A secondary mutation	42	-
GIST T1	GIST	Primary in-frame deletion in exon 11 in KIT	3.2	2.6
GIST T1 5R	GIST	Primary in-frame deletion in exon 11 in KIT, T670I secondary mutation	134	141
GIST T1 Juke	GIST	Primary in-frame deletion in exon 11 in KIT, D816E secondary mutation	23	14
Kasumi-1	AML	KIT N822K mutation	3.4	2.5
P815		Mouse mastocytoma, KIT C814Y mutation	24	41
MV-4-11	AML	FLT3-internal duplication mutation	60	12
M-NFS-60		Mouse myelogenous leukemia	59	96
A375	Melanoma	BRAF V600E mutation	410	710
HT-29	Colon	BRAF V600E mutation	230	510
COLO-205	Colon	BRAF V600E mutation	3300	3600
SK-MEL-28	Melanoma	BRAF V600E mutation	2300	10000
HCT-116	Colon	KRAS G13D mutation	580	690
SK-MEL-2	Melanoma	NRAS Q61R mutation	1300	940

Source: Data summarized from Study DCC-2618-02-0005, DCC-2618-02-0010

B. In Vivo Studies

To evaluate the anti-cancer activity of ripretinib, exon 11 deleted KIT mutant GIST T1 human gastric carcinoma cells were implanted subcutaneously into female Crl:NU-*Foxn1*^{nu} mice on Day 0 (Study DCC-2618-02-0032). On Days 21 to 30, ripretinib was administered to the mice orally, twice daily, at doses of 25 and 50 mg/kg. Control animals received vehicle. Tumor size was assessed using fluorodeoxyglucose-positron emission tomography (FDG-PET) on Days 24 and 30 and by caliper measurement three times weekly. Ripretinib (b) (4) inhibited tumor growth in a dose-dependent manner compared to vehicle control.

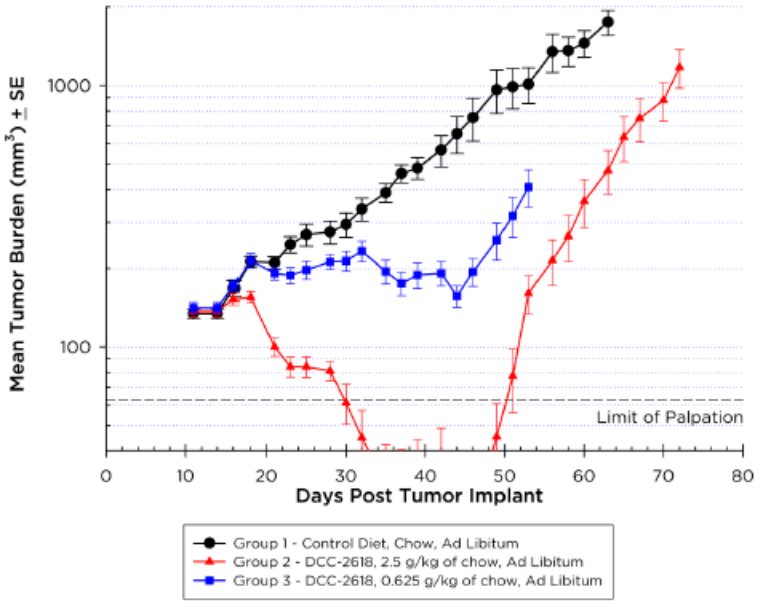
Ripretinib-induced inhibition of KIT-driven tumor growth in nu/nu mice



Source: Applicant Figure reproduced from Study DCC-2618-02-0032

To further evaluate the anti-tumor activity of ripretinib, H1703 PDGFRα-amplified human non-small cell lung cancer cells were implanted subcutaneously in the right high axilla of female Crl:NU-*Foxn1*^{nu} mice on Day 0 (Study DCC-2618-02-0049). On Days 11 to 42, ripretinib (DCC-2618) was administered to the mice formulated into the diet to achieve approximately 25 or 100 mg/kg/day. Control animals received vehicle diet. On Day 43 all animals were placed on the control diet for 13 (low dose) or 30 (high dose) days to monitor tumor regrowth. Tumor size was assessed using caliper measurements three times weekly. Ripretinib inhibited tumor growth in a dose-dependent manner compared to vehicle control, and complete tumor regression was observed in 8/10 mice at the high dose and 2/10 mice at the low dose.

Ripretinib (DCC-2618)-induced inhibition of PDGFRα amplified tumor growth in nu/nu mice



Source: Applicant Figure reproduced from Study DCC-2618-02-0049

Secondary Pharmacology

Ripretinib was assessed for its off-target profile in vitro in large kinase panels and a panel of human receptors, ion channels, transporter proteins, and enzymes.

When summarizing data from all kinase studies, including those where approximate cellular concentrations of ATP were used (1-4 mM ATP), ripretinib had > 50-fold selectivity versus the vast majority of tested kinases (approximately 300 tested kinases total). Ripretinib inhibits five kinases within 10-fold of its half maximal inhibitory concentration (IC_{50}) value for KIT kinase, including PDGFRA, and 15 kinases within 50-fold of its IC_{50} value for KIT kinase.

In cellular studies, ripretinib inhibited kinase phosphorylation of TIE2, CSF-1R, PDGFRA, PDGFRB, and VEGFR2 within 10-fold of cellular inhibition of KIT. Ripretinib moderately inhibited cellular proliferation of cells driven by FLT3 or CSF1R, and more weakly inhibited cell growth driven by RAF kinases. Ripretinib was evaluated versus a battery of 135 receptors, ion channels, and enzymes. Among the battery of 104 receptor binding assays profiled, the following afforded results wherein ripretinib inhibited binding by > approximately 80% when evaluated at 10 µM concentration: 5-HT1a (agonist radioligand), 5-HT4e (antagonist radioligand), and α2c (antagonist radioligand). Titration of these receptors afforded IC_{50} values of 610 nM, 620 nM, and 330 nM, respectively, >100-fold higher than the in vitro IC_{50} value for KIT kinase. Among the 31 enzyme and uptake assays, >80% inhibition of Abl, Fyn, and p38α kinases by ripretinib was observed. These kinases were tested in kinase studies described above at 1-4 mM ATP cofactor

concentration to obtain IC_{50} values of > 3300 nM, 1700 nM, and 615 nM, respectively. There were no off-target liabilities (potential side effects, off-target pharmacology, or toxicity) that were considered to preclude human development.

The Regulatory Authorities' Assessment:

The Regulatory Authorities generally agree with the study results described above.

Additional study results are summarized below.

In an assay screen utilizing a coupled spectrophotometric assay, which measures kinase activity by the indirect measurement of the production of ADP, ripretinib was found to inhibit numerous kinases with IC_{50} values of less than 10 nM (Study DCC-2618-02-0029):

Kinase	IC_{50} value (nM)
KIT	3
BRAF	4.9
CRAF	3.3
FLT3	3.3
FMS	3.7
KDR	8.7
LCK	5.5
LYN	20
p38α	9.5
TIE2	61

Source: Data summarized from Study DCC-2618-02-0029

In this assay, ripretinib also inhibited FGFR1 and BRAF V600E with IC_{50} values of 45 and 48 nM, respectively.

In a panel of 295 kinase assays, ripretinib inhibited ARAF, BRAF, DDR2, EPHA2/4/5, EPHB1/2, FMS, FRK, HIPK4, LYN, PDGFRα, PDGFRβ, RAF1, RET, TAOK2/TAO1, and ZAK within 10-fold of the KIT kinase IC_{50} value of 3.0 nM (Study DCC-2618-02-0030). This screen utilized ATP levels of 0.01 mM, which is much lower than physiological ATP levels. A secondary screen was performed using higher levels of ATP (Study DCC-2618-02-0044). At 4 mM ATP, only FMS and DDR2 were inhibited within 10-fold of the IC_{50} value for KIT, and ripretinib was 10 to 50-fold selective for KIT versus EPHB2, FLT4, KDR, LCK, LYN, MYLK2, PDGFRα, PDGFRβ, p38β, TAOK2, TRKA, and ZAK, and >50-fold selective for all other kinases tested.

Safety Pharmacology

Respiratory function

In a respiratory safety study, ripretinib given at 15, 60, or 300 mg/kg mildly decreased tidal volume by 10% at 15 mg/kg and up to 17% at 300 mg/kg in rats. The observed changes in tidal volume were not considered physiologically important because they were transient and of small magnitude.

Central nervous system (CNS) function

Ripretinib given at 15, 60, or 300 mg/kg had no effect on any component of the modified Irwin battery of behavioral testing at any measured time point in rats.

Cardiovascular function

In vitro: The Predictor™ hERG Fluorescence Polarization Assay (b) (4) was used to assess hERG channel binding potential in a homogenous, fluorescence polarization (FP)-based format. The average hERG IC_{50} value = 7.9 µM for ripretinib. Given the single- and double-digit nanomolar inhibition of KIT and PDGFRα mutants in vitro, the high concentrations required for inhibition of the hERG channel in this assay would likely result in negligible inhibition in vivo.

In vivo: Single doses of ripretinib in beagle dogs in a CV safety study resulted in marked increase in HR (up to 129% at 75 mg/kg) with secondary decreases in QT and PR interval in animals given ≥ 7 mg/kg from 9 hours post dose through 19 hours post dose and increased diastolic and mean arterial pressure in animals given ≥ 7 mg/kg through 6 hours post dose. There were no changes to systolic pressures or arterial pulse pressure. QTc values were not significantly increased with ripretinib treatment. Heart rates remained elevated at the end of the telemetry collection (19 hours post dose), but differences were slightly less suggesting that heart rates were beginning to recover at 19 hours post dose. The magnitudes of the blood pressure and heart rate changes were considered noteworthy, but not considered to represent a severe toxicity.

<u>The Regulatory Authorities' Assessment:</u>

The Regulatory Authorities generally agree with the study results described above.

Additional study results are summarized below.

Respiratory function (Study DCC-2618-02-0025): Ripretinib administration decreased tidal volume in a dose-dependent manner by -10%, -13%, and -17% at 15, 60, and 300 mg/kg, respectively, as compared to controls. The effect on tidal volume recovered by 24 hours post-dose. Ripretinib had no effect on any other respiratory parameter measured.

Cardiac function (Study DCC-2618-02-0043): Female Beagle dogs (n=4) were administered a single 7, 20, or 75 mg/kg dose of ripretinib. Ripretinib-related changes in CV parameters are summarized below, as % change from the control group.

CV parameter	Dose (mg/kg)		
	7	20	75
Heart rate	45	70	129
QT interval	-5	-6	-8
PR interval	-9	-12	-16
Diastolic pressure	12	12	17
Mean arterial pressure	7	6	9

Source: Data summarized from Study DCC-2618-02-0043

5.4. ADME/PK

Type of Study	Major Findings
Absorption	
Absorption, Metabolism, and Excretion of ^{14}C-ripretinib Following 25 mg/kg Oral or 1 mg/kg IV Administration to Dogs (Study DCC-2618-03-0038)	Ripretinib is a low-solubility and moderate permeability compound and exhibits moderate oral absorption. ^{14}C-Ripertinib oral administration resulted in T_{max} ranging from 3 to 4 hours, a rapid elimination half-life of 1.17 hours in plasma and a calculated oral bioavailability of ~27% in beagle dogs.
Distribution	
Pharmacokinetics, Distribution, Metabolism, and Excretion of ^{14}C- ripretinib Following Oral Administration to Rats (Study DCC-2618-03-0037)	Radiolabeled [^{14}C] ripretinib was extensively bound to melanin-containing tissues in pigmented Long Evans (LE) rats such as eye ciliary body, eye uveal tract, and eyes, and the radiolabel binding showed a long half-life. In non-pigmented Sprague Dawley (SD) rats, binding to these regions was minor. The distribution in plasma, liver, and kidney in SD rats show half-lives of 4.4 hours, 11.7 hours, and 13.6 hours. Similarly, in the LE rat, the distribution in plasma, liver, and kidney show half-lives of 4.2 hours, 10.7 hours, and 12.6 hours, respectively. However, in SD rats low levels of radioactivity persisted with long half-lives of 31 and 32.5 hours in blood and cecum, respectively. Brain penetration by ripretinib was low. Measurable but low levels of radioactivity were present beyond 168 hrs post dose in whole body autoradiography in LE rats. Dosimetry assessment demonstrated whole-body radiation exposure was 0.751 mrem, and the single exposure Percent Limit was 0.025%.
Metabolism	
Metabolite Profiling of ripretinib in Mouse, Rat, Dog, Monkey and Human Hepatocytes (Study DCC-2618-03-0012)	Ripretinib and 5 related components (M1 through M5) were detected in incubations of mouse, rat, dog, monkey, and human hepatocytes with 10 µM ripretinib. Ripretinib metabolite profiling in hepatocytes from human, mouse, dog, and monkey hepatocytes showed qualitative similarities. The monkey profile most closely matched the human hepatocyte

Type of Study	Major Findings
	profile. No human-specific or human-disproportionate metabolites were observed. Metabolite M5, the N-des-methyl ripretinib, (DP-5439), was the major active metabolite produced in vitro in all 5 species. The remaining metabolites, two oxidation products and their sulfate conjugates, ranged from <1% to 5%. In vivo, unchanged ripretinib and active metabolite M5 (DP-5439) were the major circulating components in plasma accounting for 51 -71% and 22-38%, respectively, following oral dosing in rats and dogs.
Excretion	
Pharmacokinetics, Distribution, Metabolism, and Excretion of ^{14}C- ripretinib Following Oral Administration to Rats (Study DCC-2618-03-0037)	Following a single oral dose of ^{14}C-ripretinib, fecal elimination of radioactivity was the major elimination pathway in intact males and females and bile-duct cannulated (BDC) males, with approximately 85% to 88% in intact males and females and 56% of the administered dose in BDC males recovered in feces. Hepatobiliary excretion was a significant route of elimination of absorbed radioactivity, with approximately 13% of the administered dose recovered in bile. Renal excretion was a minor route of elimination, with approximately 1% to 4% of the dose recovered in urine from SD and BDC rats.
TK data from general toxicology studies 4-Week Toxicity and Toxicokinetic Oral Gavage Study of DCC-2618 in Rats with a 4-Week Recovery Phase (Study DCC-2618-04-0004) 13-Week Oral Gavage Toxicity and Toxicokinetic Study with ripretinib in Rats with a 4-Week Recovery Phase (Study DCC-2618-04-0006)	In the 4 and 13 week Toxicity study in rats, ripretinib exposures generally increased with dose levels up to 300 mg/kg/day but were less than dose proportional with oral doses up to 300 mg/kg/day. Exposures were higher in females than in males. Exposures on Day 28 and 91 were consistently lower than seen on Day 1. Similarly, active metabolite DP-5439 levels were less than dose proportional with increase in dose. Metabolite to parent ratios ranged from 0.15 to 0.44 in 4 week and 0.16 to 0.29 in 13 week studies. The no observed adverse effect levels (NOAELs) for ripretinib in the 4 and 13 Week studies were 300 and 100 mg/kg/day, respectively.
TK data from reproductive toxicology studies A Pivotal Embryo-Fetal Development Study of ripretinib by Oral (Gavage) in Rats (DCC-2618-04-0013) A Dose Range-Finding Embryo-Fetal Development Study of ripretinib by Oral (Gavage) in Rabbits (Study DCC-2618-04-0012)	In pregnant rats, exposure to ripretinib generally increased with dose; increases in C_{max} were in general less than dose proportional, while increases in area under the concentration-time curve from 0 to time "t" (AUC_{0-t}) were dose-proportional when dose increased from 1 to 5 mg/kg/day and between 5 and 20 mg/kg/day. In rat, the AUC_{0-t} (on gestation day [DG] 11) at the maternal NOAEL was 1260 hr*ng/mL at 5 mg/kg/day. This is consistent with what was seen in other repeat-dose toxicology studies in rats, suggesting that the pharmacokinetics of ripretinib are similar in both pregnant and non-pregnant SD rats. Similarly, in pregnant rabbits, exposure to ripretinib increased dose proportionally when dose increased from 2 to 10 mg/kg/day and 10 to 40 mg/kg/day, but less than dose proportional when dose increased from 40 to 150 mg/kg/day.

Type of Study	Major Findings
	In rabbit, the 40 mg/kg/day resulted in plasma C_{max} of 4530 ng/mL and AUC_{0-t} of 48900 ng*hr/mL on DG 13.

Abbreviations: BDC = Bile-Duct Cannulated; DG = Gestation day; LE = Long-Evans; NOAEL = No observed adverse effect level; SD = Sprague-Dawley.

The Regulatory Authorities' Assessment:

The Regulatory Authorities generally agree with the study results described above.

Additional study results are summarized below.

Absorption:
In vitro protein binding of ripretinib was assessed in pooled, cryopreserved, mixed gender mouse, rat, dog, monkey, and human plasma at a concentration of 2 µM. Plasma protein binding % data is summarized below (Study DCC-2618-03-0023).

Mouse	99.86%
Rat	99.90%
Dog	99.86%
Monkey	99.87%
Human	99.93%

Source: Data summarized from Study DCC-2618-03-0023

The pharmacokinetics of single dose ripretinib studies are summarized below. A single oral dose of 25 mg/kg was used in the rat and dog studies.

Parameter (blood)	SD Rats (Study DCC-2618-03-0037)		Beagle Dogs (Study DCC-2618-03-0038)	
	Male	Female	Male	Female
C_{max} (ng/mL)	2020	2890	846	620
AUC (ng·h/mL)	23200	33300	2690	2060
$T_{1/2}$ (hours)	6	8	N/A	4.4

Source: Data summarized from Study DCC-2618-03-0037, DCC-2618-03-0038

Distribution:
In a single dose study of radiolabeled [^{14}C] ripretinib in Sprague Dawley rats (Study DCC-2618-03-0037), ripretinib was present in most tissues by 4 hours post-dose and reached C_{max} by 4-8 hours. At the last sampling of 672 hours post-dose, ripretinib was still present in the eye and eye uveal tract. The tissues with the highest ripretinib exposure were liver, adrenal gland, and

kidney.

To examine CNS penetration, Sprague Dawley rats were administered a single intravenous dose of 0.9 mg/kg (Study DCC-2618-03-0033). CNS distribution data is summarized below.

Parameter	CNS, Rat	
	Plasma	Brain
C_{max} (ng/mL)	712	25.8
AUC (ng·h/mL)	1080	23.8
$T_{1/2}$ (hours)	1.62	N/A

Source: Data summarized from Study DCC-2618-03-0033

Excretion:
The mean percent of radioactive ripretinib recovered 120- or 168-hours post-dose is summarized below (Study DCC-2618-03-0037).

	Mean Percent of Dose					
	Intact (0-168 hour)				BDC (0-120 hours)	
Matrix	Male	SD	Female[a]	SD	Male	SD
Urine	1.58	0.208	1.67	NA	4.44	NA
Feces	89.3	3.13	85.7	NA	56.6	NA
Bile	NA	NA	NA	NA	13.6	NA
Total[b]	92.6	2.38	91.0	NA	77.9	NA

BDC = bile duct-cannulated; NA= not applicable.
a Values are presented as the average (N = 2).
b For 0-120 hour BDC animals, total includes radioactivity from urine, feces, cage rinse, cage wash, cage wipe, bile, bile cannula, jacket rinse, and residual carcass; for 0-168 hour intact animals, total includes radioactivity from urine, feces, cage rinse, cage wash, cage wipe, and residual carcass.

Source: Applicant Figure reproduced from Study DCC-2618-03-0037

Toxicokinetics:
Exposure of ripretinib is less than dose-dependent and is generally similar between sexes. Toxicokinetic data of ripretinib and major metabolite DP-5439 from the chronic and embryo-

fetal developmental toxicology studies is summarized below.

Ripretinib				DP-5439			
13-week rat study, Day 91				13-week rat study, Day 91			
Dose	30	100	300	Dose	30	100	300
C_{max} (ng/mL)	1350	2640	2380	C_{max} (ng/mL)	393	736	558
$AUC_{0\text{-}24}$ (ng-h/mL)	11000	20800	21400	$AUC_{0\text{-}24}$ (ng-h/mL)	2800	5530	5890
$t_{1/2}$ (h)	7.52	4.06	4.64	$t_{1/2}$ (h)	6.71	3.94	3.65
13-week dog study, Day 91				13-week dog study, Day 91			
Dose	2.5	5	10	Dose	2.5	5	10
C_{max} (ng/mL)	421	511	905	C_{max} (ng/mL)	122	126	235
$AUC_{0\text{-}24}$ (ng-h/mL)	1390	1910	3420	$AUC_{0\text{-}24}$ (ng-h/mL)	414	425	873
$t_{1/2}$ (h)	2	4.38	1.9	$t_{1/2}$ (h)	N/A	N/A	N/A
Rat embryo-fetal toxicity study, DG 11				Rat embryo-fetal toxicity study, DG 11			
Dose	1	5	20	Dose	1	5	20
C_{max} (ng/mL)	31.2	45.9	75	C_{max} (ng/mL)	0	46.7	198
$AUC_{0\text{-last}}$ (ng-h/mL)	184	1260	9410	$AUC_{0\text{-last}}$ (ng-h/mL)	N/A	195	888
Rabbit embryo-fetal toxicity study, DG 13				Rabbit embryo-fetal toxicity study, DG 13			
Dose	2	10	40	150	Dose	2	10	40	150
C_{max} (ng/mL)	260	1410	4530	7320	C_{max} (ng/mL)	22	120	458	685
$AUC_{0\text{-last}}$ (ng-h/mL)	1640	11200	48900	81200	$AUC_{0\text{-last}}$ (ng-h/mL)	89	1280	5910	8820

Source: Data summarized from Study DCC-2618-04-0006, DCC-2618-04-007, DCC-2618-04-0013, DCC-2618-04-0012

5.5. Toxicology

5.5.1. General Toxicology

The Applicant's position:

Ripretinib is intended for the treatment of patients with advanced malignancies driven by KIT/PDGFRA activating mutations. The toxicology studies were designed in accordance with ICH S9 guidance, as well as with all other relevant International Conference on Harmonization (ICH) guidances on safety. All principal toxicology studies were conducted in accordance with good laboratory practice (GLP) and currently accepted guidelines.

Ripretinib was tested in repeated-dose studies in rats and dogs of 2 (non-GLP, dose-range finding), 4 (GLP) and 13 weeks (GLP) of treatment duration. 13-week studies are described in detail below and the results of the 4-week studies summarized.

Study title/ Study number: 13-week repeated dose toxicology study with recovery in rats/ Study DCC-2618-04-0006

Key Study Findings

- Ripretinib was well tolerated at doses of 30 and 100 mg/kg/day, with adverse changes occurring at 300 mg/kg/day. The NOAEL for ripretinib was 100 mg/kg/day.

- Sprague Dawley rats showed missing/discoloration of the growing incisor teeth (300 mg/kg/day only), discolored skin and skin lesions (≥30 mg/kg/day), alopecia or thinning hair coat, decreased body weight and body weight gain, and decreased food consumption (females only at 300 mg/kg/day).
- Three animals administered 300 mg/kg/day were sacrificed at an unscheduled interval for humane reasons due to the clinical observation of skin lesions.

Conducting laboratory and location: (b) (4) (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 30, 100, or 300 mg/kg/day, daily dosing

Route of administration: oral gavage

Formulation/Vehicle: (b) (4) ripretinib in HPMCAS (b) (4) (b) (4) methylcellulose (b) (4) in reverse osmosis water

Species/Strain: Sprague-Dawley rats

Number/Sex/Group: 10/sex/group (recovery: 5/sex/group included at 0, 100, and 300 mg/kg/day and left untreated for 4 weeks)

Age: 6 to 7 weeks old

Satellite groups/ unique design: None

Deviation from study protocol affecting interpretation of results: No

Observations and Results: changes from control

Parameters	Major findings
Mortality	Three animals administered 300 mg/kg/day (one toxicity male, one TK male, and one TK female) were sacrificed in moribund condition on Day 22 or 29 of the dosing phase due to ripretinib-related clinical observations of discolored skin, scabs on the tail and/or feet, scaly skin on the tail, and thinning hair coat.
Clinical Signs	Clinical observations included missing and white teeth, swollen feet, thin appearance, clear oral discharge, discolored and/or scaly skin on the feet and tail, piloerection and rough hair coat, scabs and/or sores on the feet/tail/ear, and alopecia or thinning hair coat. Recovery was noted for the scaly skin, thinning hair coat, and sores and scabs during the recovery period.
Body Weights	Decreased body weight and decreased body weight gain and decreased food consumption (in females only at 300 mg/kg/day) were observed at

Parameters	Major findings
	all doses. These findings partially, but not completely, reversed during the recovery phase.
Ophthalmoscopy	No relevant treatment-related changes.
Hematology	Hematology and coagulation findings suggestive of red blood cell loss included minimally lower red cell mass (red blood cell count, hemoglobin concentration, and/or hematocrit) in animals administered ≥ 100 mg/kg/day. Mildly higher mean corpuscular volumes in males administered ≥ 100 mg/kg/day and females administered ≥ 30 mg/kg/day. Mildly higher mean corpuscular hemoglobin in animals administered ≥ 30 mg/kg/day. Mildly higher red cell distribution width (RDW) in males administered ≥ 100 mg/kg/day and females administered ≥ 30 mg/kg/day. Mildly higher reticulocyte counts in females administered ≥ 100 mg/kg/day. The increased RDW and reticulocyte counts suggest a compensatory response to the lower red cell mass. Indications of inflammatory response included minimally to mildly higher white blood cell, neutrophil, and platelet counts in animals administered ≥ 30 mg/kg/day; minimally higher monocyte and large unstained cell counts in males administered ≥ 100 mg/kg/day and females administered ≥ 30 mg/kg/day; minimally higher eosinophil count in males administered ≥ 30 mg/kg/day and females administered ≥ 100 mg/kg/day; minimally higher basophil count in females administered ≥ 100 mg/kg/day; and mildly higher fibrinogen concentration in animals administered ≥ 30 mg/kg/day. Changes correlated with macroscopic/microscopic skin findings. Mildly lower lymphocyte counts in males administered 300 mg/kg/day were suggestive of a stress response.
Clinical Chemistry	Minimally to mildly lower total protein and albumin concentrations in animals administered ≥ 30 mg/kg/day; mildly lower albumin:globulin ratio in animals administered ≥ 100 mg/kg/day; and minimally lower calcium concentration (reflective of decreased albumin) in animals administered ≥ 30 mg/kg/day. Minimally higher alanine aminotransferase (ALT) activity in males administered ≥ 30 mg/kg/day and females administered ≥ 100 mg/kg/day and minimally increased alkaline phosphatase (ALP) activity in females administered 300 mg/kg/day. Minimally to mildly higher total bilirubin concentration was observed in females administered ≥ 30 mg/kg/day and was likely unrelated to the microscopic liver findings. Minimally to mildly lower glucose concentration in animals administered ≥ 30 mg/kg/day, minimally higher urea nitrogen concentration in males administered ≥ 100 mg/kg/day, mildly lower cholesterol concentration in males administered ≥ 100 mg/kg/day and females administered ≥ 30 mg/kg/day, minimally lower phosphorus concentration in males administered ≥ 30 mg/kg/day and females administered ≥ 100 mg/kg/day, and minimally lower alkaline phosphatase activity in males administered 300 mg/kg/day and females administered 100 mg/kg/day (all possibly resulting from decreased food consumption).
Urinalysis	No relevant treatment-related changes.

Parameters	Major findings
Gross Pathology	Small testes in males. Minimal to marked degeneration of the teeth in females and males. Marked degeneration of Brunner's glands of the proximal duodenum at 300 mg/kg/day, considered adverse in 2 females.
Organ Weights	Decreased testis and epididymis weights in males at 300 mg/kg/day.
Histopathology	Partially reversible minimal to moderate hypertrophy/hyperplasia of blood vessels in liver, lungs, and/or mesenteric lymph node at ≥ 100 mg/kg/day. Reversible minimal to moderate hyperplasia/hyperkeratosis of the epidermis of the skin/subcutis and squamous epithelium of the tongue, esophagus, and/or nonglandular stomach at ≥ 30 mg/kg/day. Minimal to slight hyperplasia of the transitional epithelium of the urinary bladder at ≥ 30 mg/kg/day, that was seen at a similar incidence/severity in recovery animals administered ≥ 100 mg/kg/day. Increased osteoblastic surface and/or decreased trabeculae of the femur at ≥ 30 mg/kg/day. Changes generally decreased in incidence and/or severity in recovery sacrifice animals administered ≥ 100 mg/kg/day, suggesting partial reversibility and newly formed trabeculae in the femoral bone of recovery sacrifice animals were similar to those of control animals.
Other evaluations	None

Abbreviations: SD = Sprague-Dawley; LE = Long-Evans; f = female; m = male.

4-Week Repeated-Dose Toxicology Study with Recovery in Rats (Study DCC-2618-04-0004)

Daily oral treatment of male and female Sprague Dawley rats at dose levels of 15, 60, and 300 mg/kg/day for 4 weeks was generally well tolerated with only minor effects on body weight and food consumption. The NOAEL for ripretinib after 4 weeks of dosing was 300 mg/kg/day. Reversible major clinical pathology changes included decreased red blood cell count, hemoglobin, and hematocrit, higher platelet count, higher white blood cell count, higher absolute neutrophil count, higher monocyte and large unstained cell counts, lower protein, lower albumin, lower calcium, lower glucose, and lower cholesterol. Ripretinib-related microscopic changes were present in the non-glandular stomach (diffuse hyperplasia/hyperkeratosis) of animals given ≥ 60 mg/kg/day. This finding partially reversed during the recovery phase but was still present in females given 300 mg/kg/day. Based on the minimal to slight severity and the lack of effect on the overall health of animals, hyperplasia/hyperkeratosis of the nonglandular gastric epithelium was not considered adverse. It also should be noted that nonglandular stomach is not found in humans and therefore, this finding was deemed of no relevance for clinical trials with ripretinib.

Study title/ Study number : 13-week repeated dose toxicology study with recovery in dogs/ Study DCC-2618-04-0007

Key Study Findings

• Ripretinib-related clinical observations were seen at all dose levels and included decreased body weight gain, decreased food consumption, skin lesions, thinning hair coat, and clinical pathology changes observed at all doses were consistent with an inflammatory and/or stress response. The NOAEL for ripretinib after 13 weeks of dosing was 5 mg/kg/day.
• Skin changes (including skin lesions and thinning hair coat/hair loss), dose-related in severity, were noted at all doses (2.5, 5, and 10 mg/kg/day).
• All changes reversed during the recovery phase except discolored skin.

Conducting laboratory and location: (b) (4) (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 2.5, 5, 10 mg/kg/day, daily dosing

Route of administration: oral gavage

Formulation/Vehicle: (b) (4) ripretinib in HPMCAS (b) (4) (b) (4) methylcellulose (b) (4) in reverse osmosis water

Species/Strain: beagle dog

Number/Sex/Group: 5/sex/group

Age: 5-6 months

Satellite groups/ unique design: None

Deviation from study protocol affecting interpretation of results: No

Observations and Results: changes from control

Parameters	Major findings
Mortality	No mortality, but one female administered 10 mg/kg/day was sacrificed in a moribund condition on Day 23 of the dosing phase due to body weight loss, poor body condition, inflamed skin around the eyes, and redness and swelling of the muzzle and paws. This dog lost 0.8 kg of body weight during the acclimation period prior to the first dose of ripretinib and began receiving canned food on Day 1 of the study. Despite the use of canned food and dietary enrichments (ex. peanut butter) she ate poorly and continued to lose weight. Unclear whether death was due to direct ripretinib toxicity as the animal was already in a weakened state due to poor acclimation and low food consumption prior to the dosing phase, which likely was exacerbated by the test article.
Clinical Signs	Clinical observations at all dose levels included skin lesions (broken and/or discolored or scaly skin and/or scabs or sores or raised areas) and thinning hair coat. Swollen limbs, thin appearance, and fecal abnormalities at ≥ 5 mg/kg/day. During the recovery phase the skin lesions resolved with the exception of discolored skin. Animals regained their hair and no longer felt warm to the touch when ripretinib treatment was discontinued. Dogs at 10 mg/kg/day were given antibiotics and non steroidal anti inflammatory drugs (NSAIDs) starting from Week 6 until terminal necropsy due to the severity of their skin lesions.
Body Weights	Decreased body weight gain and decreased food consumption observed at all dose levels.
Ophthalmoscopy	No relevant treatment-related changes.
ECG	No relevant treatment-related changes.
Hematology	At 10 mg/kg/day, minimally to mildly increased white blood cell and/or neutrophil counts on Days 28, 56, and/or 92 in males. At 10 mg/kg/day minimally increased platelet counts on Day 92 in males and females. At 5mg/kg/day, minimally to mildly increased fibrinogen concentration on

Parameters	Major findings
	Day 56 in males. At 10 mg/kg/day minimally to mildly increased fibrinogen noted in males on Day 92.
Clinical Chemistry	Mildly decreased albumin concentration on Day 92 in females at ≥ 5 mg/kg/day, and mildly increased globulin concentration on Days 28 (males only), 56, and/or 92 in males at ≥ 2.5 mg/kg/day and females at 10 mg/kg/day. Minimally decreased albumin:globulin ratio also was observed on Days 28 (males only), 56, and 92 in males administered ≥ 2.5 mg/kg/day and females administered ≥ 5 mg/kg/day. These findings exhibited evidence of reversibility at the end of the recovery phase and were considered not adverse based on their small magnitude.
Urinalysis	No relevant treatment-related changes.
Gross Pathology	Alopecia, discolored, scab, scaly skin, sore, and/or thickened.
Organ Weights	No relevant treatment-related changes.
Histopathology	Microscopic findings were present in multiple regions of the skin/subcutis of animals administered ≥ 5 mg/kg/day (minimal to moderate hyperplasia/hyperkeratosis, minimal to slight mixed cell inflammation, and minimal to moderate erosion/ulcer and crust, minimal congestion/hemorrhage, and moderate atrophy of adipocytes). At 2.5 mg/kg/day microscopic findings in the skin/subcutis of animals was limited to minimal hyperplasia/hyperkeratosis. Skin/subcutis changes reversed when ripretinib treatment was discontinued.

4-Week Repeated-Dose Toxicology Study with Recovery in Dogs (Study ripretinib-04-0005)

Daily treatment of male and female beagle dogs at dose levels of 7 mg/kg/day for 4 weeks was generally well tolerated, but doses of 20 and 75 mg/kg/day resulted in serious skin changes requiring use of topical antibiotics, steroids, and/or meloxicam (NSAID), discontinuation of dosing and/or early sacrifice. The NOAEL for ripretinib after 4 weeks of dosing was 7 mg/kg/day. Minor effects on body weight, food consumption, and clinical pathology occurred in the study, but were of insufficient magnitude at any dose of ripretinib to be considered adverse. Microscopic changes were limited to the skin, reduced lymphocytes in lymphoid tissues, and minimal cytoplasmic rarefaction of hepatocytes at 20 and 75 mg/kg/day. No significant microscopic changes were noted at 7 mg/kg/day and changes seen at 20 and 75 mg/kg/day showed partial or complete reversal during the 28-day recovery phase of the study. No bone marrow changes were seen at any dose of ripretinib, including 20 and 75 mg/kg/day that resulted in early termination of dogs due to serious skin reactions.

<u>The Regulatory Authorities' Assessment:</u>

The Regulatory Authorities generally agree with the study results described above.

Additional study results are summarized below.

13-week repeated dose toxicology study with recovery in rats/ Study DCC-2618-04-0006

Key Study Findings:

- Daily administration of ripretinib resulted in discolored skin and skin lesions, alopecia or thinning hair coat, decreased body weight or body weight gain at doses of ≥ 30 mg/kg
- Main target organs of toxicity were skin, teeth, and lung. These findings trended toward reversibility in the recovery period
- Adverse findings of the testes and epididymis were observed and did not reverse within the recovery period

Mortality: One TK group male that was euthanized on Day 29 in moribund condition had microscopic observations of marked hemorrhage and neutrophilic inflammation in the urinary bladder with likely extension to the kidney
Clinical observations: a new observation of white teeth was made during the recovery phase
Food consumption: Decreased food consumption was observed for males administered ≥100 mg/kg/day but was not observed for females administered ≤100 mg/kg/day.
Hematology: The severity of ripretinib-related hematology changes is summarized below.

	Males			Females		
	30 mg/kg	100 mg/kg	300 mg/kg	30 mg/kg	100 mg/kg	300 mg/kg
Parameter	Percent change from control					
Basophils	12%	15%	14%	21%	63%	90%
Eosinophils	114%	134%	188%	22%	64%	118%
Large Unstained	55%	147%	208%	103%	192%	264%
Leukocytes	41%	57%	49%	38%	76%	99%
Lymphocytes	-3%	-17%	-32%	2%	15%	33%
Monocytes	24%	81%	132%	74%	136%	161%
Neutrophils	209%	330%	330%	221%	388%	429%

Source: Data summarized from Study DCC-2618-04-0006

Clinical chemistry: The severity of ripretinib-related clinical chemistry changes is summarized below.

	Males			Females		
	30 mg/kg	100 mg/kg	300 mg/kg	30 mg/kg	100 mg/kg	300 mg/kg
Parameter	Percent change from control					
ALT	30%	27%	31%	4%	61%	114%
Albumin	-8%	-13%	-13%	-12%	-19%	-26%
A:G	-1%	-6%	-2%	-8%	-23%	-30%
AST	12%	0%	20%	-13%	25%	43%
Bilirubin	37%	22%	41%	143%	390%	367%
ALP	13%	5%	-6%	-3%	10%	23%
Protein	-8%	-10%	-11%	-9%	-11%	-15%

Source: Data summarized from Study DCC-2618-04-0006

Microscopic observations: Additional histopathology observations are summarized below.

Sex		Male				Female			
Dose (mg/kg		0	30	100	300	0	30	100	300
#Examined (Main/Recovery)		11/4	10/0	10/5	10/5	10/5	10/0	10/5	10/5
Lung									
Hypertrophy/hyperplasia, bronchiolar epithelium	MINIMAL		6	5	9		5	6	9/3
Hypertrophy/hyperplasia, vessel	MINIMAL			2	2/1				1
	MILD				1				
Vacuolation, bronchiolar epithelium	MINIMAL		8	6/4	8/3	0/1	9	5/3	4/4
	MILD		1					1	5/1
Tooth, Incisor									
Degeneration	MINIMAL				1		1	4	3/1
	MILD				2			1	6
	MODERATE							1	5
	MARKED								1
Small intestine, Duodenum									
Degeneration, Brunner's glands	SEVERE								2
Testis									
Degeneration/Atrophy, seminiferous epithelium, bilateral	MINIMAL	1	4	2	2/1				
	MILD			0/1	1/1				
	MODERATE				2/1				
	MARKED				1				
Epididymis									
Debris, cellular, bilateral, increased	MINIMAL		3		1/1				
	MILD				2				
	MODERATE				2/1				
	MARKED				1				

Source: Data summarized from Study DCC-2618-04-0006

13-week repeated dose toxicology study with recovery in dogs/ Study DCC-2618-04-0007

Clinical signs: animals dosed at ≥ 5 mg/kg felt warm to the touch on the entire body or head during the dosing period

Body weight: Body weights in animals dosed at 2.5, 5, and 10 mg/kg/day were -9%, -13% and -20% of controls at the end of the dosing period, respectively. Body weight gain trended towards recovery.

Hematology: The severity of ripretinib-related hematology changes is summarized below

	Males			Females		
	2.5 mg/kg	5 mg/kg	10 mg/kg	2.5 mg/kg	5 mg/kg	10 mg/kg
Parameter	Percent change from control					
Basophils	-35%	-31%	4%	126%	11%	32%
Eosinophils	6%	42%	24%	-19%	26%	68%
Large Unstained Cells	-29%	-25%	38%	86%	14%	43%
Leukocytes	0%	10%	41%	37%	23%	38%
Lymphocytes	3%	6%	-3%	49%	17%	33%
Monocytes	-15%	5%	19%	2%	1%	60%
Neutrophils	1%	11%	70%	36%	27%	38%
Platelets	22%	28%	55%	49%	28%	47%
Reticulocytes	14%	54%	39%	55%	47%	46%
Fibrinogen	4%	24%	61%	-7%	-9%	14%

Source: Data summarized from Study DCC-2618-04-0007

Clinical chemistry: The severity of ripretinib-related clinical chemistry changes is summarized below.

	Males			Females		
	2.5 mg/kg	5 mg/kg	10 mg/kg	2.5 mg/kg	5 mg/kg	10 mg/kg
Parameter	Percent change from control					
Alanine Aminotransferase	-37%	-29%	-40%	-4%	-19%	-38%
Albumin	-6%	-2%	-5%	-5%	-14%	-15%
Albumin/Globulin	-19%	-14%	-23%	-9%	-20%	-28%
Globulin	15%	11%	26%	2%	7%	17%
Alkaline Phosphatase	13%	-7%	8%	0%	-22%	-17%
Aspartate Aminotransferase	0%	-12%	-13%	5%	4%	-15%

Source: Data summarized from Study DCC-2618-04-0007

Microscopic observations: Histopathology observations are summarized below.

Sex		Male				Female			
Dose (mg/kg)		0	2.5	5	10	0	2.5	5	10
#Examined (Main/Recovery)		3/2	3/2	3/2	3/2	3/2	3/2	3/2	3/2
Skin/Subcutis									
Atrophy, adipocytes, subcutis	MODERATE								1
Congestion/hemorrhage	MINIMAL			1					
Crust	MINIMAL				1				
	MILD			1				1	1
	MODERATE			1	1			1	
Erosion/ulcer	MINIMAL				1				
	MILD				1				
	MODERATE				1			1	
Hyperplasia/hyperkeratosis	MINIMAL		1						
	MILD			1	2			1	2
	MODERATE			2	2			1	1
Hyperplasia/hyperkeratosis, epidermis	MINIMAL		1	2		1	1		3
	MILD				2				1
	MODERATE				1				1

Source: Data summarized from Study DCC-2618-04-0007

5.5.2. Genetic Toxicology

In a GLP-compliant bacterial mutation study, both ripretinib and DP 5439 (active metabolite) did not induce mutations in the 4 histidine-requiring Salmonella typhimurium strains (TA98, TA100, TA1535, and TA1537) or the tryptophan-requiring Escherichia coli strain (WP2 uvrA pKM101). In an in vivo combined micronucleus and comet assay, ripretinib did not induce micronuclei in polychromatic erythrocytes of the bone marrow, nor did it induce DNA strand breaks in the liver when tested up to 600 mg/kg/day (the maximum feasible dose).
The genotoxicity testing of ripretinib and its active metabolite DP-5439 indicate a low potential for genotoxicity. The in vitro bacterial mutagenicity, in vivo micronucleus, and in vivo comet assay indicate no significant DNA damage caused by ripretinib.

<u>The Regulatory Authorities' Assessment:</u>

The Regulatory Authorities agree with the study results described above.

Ripretinib and DP-5439 were not mutagenic in an in vitro bacterial reverse mutation (Ames) assay or clastogenic in either an in vitro human lymphocyte culture micronucleus assay or an in vivo rat bone marrow micronucleus assay.

Ripretinib and DP-5439 were tested in an in vitro micronucleus assay using human lymphocyte cultures at a concentration range from 0.5 to 300 µg/mL. In this assay, cells treated with ripretinib for 24 hours plus 24 hours recovery in the absence of S9 resulted in a statistically significant increase in the number of micronucleated binucleate cells as compared to

concurrent vehicle controls. FDA is not concerned that this increase indicates genotoxicity potential for the following reasons:

- The increase in micronucleated binucleate cells was small and only slightly outside the historical control range
- Shorter treatment conditions (3 hours plus 21 hours recovery) that explored doses of ripretinib that were approximately 10x higher were negative for micronucleus formation
- The DP-5439 data was negative, as was the in vivo assay

5.5.3. Carcinogenicity

No carcinogenicity studies have been conducted with ripretinib.

The Regulatory Authorities' Assessment:

The Regulatory Authorities agree that carcinogenicity was not warranted for the proposed indication.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

The Applicant's Position:

No fertility and early embryonic development studies have been conducted with ripretinib. Per ICH guidance S9, these studies are not warranted to support clinical trials or marketing for the treatment of patients with advanced cancer.

The Regulatory Authorities' Assessment:

The Regulatory Authorities agree that these studies were not warranted for the proposed indication.

Embryo-Fetal Development

The Applicant's Position:

Ripretinib was teratogenic in both rats and rabbits. In rats, ripretinib induced malformations primarily associated with the cardiovascular and skeletal systems at a maternal dose of 20 mg/kg/day. In rabbits, early embryonic death occurred in all rabbits at 150 mg/kg/day. The administered dose and exposure associated with developmental toxicity were within the relevant therapeutic range for ripretinib, and appropriate contraceptive measures will be required for clinical use.

Study title/ number: Embryo-Fetal Development Study of ripretinib by Oral (Gavage) in Rats /Study DCC-2618-04-0013

Key Study Findings

- Ripretinib was teratogenic at a maternal dose of 20 mg/kg/day, inducing malformations primarily associated with the cardiovascular and skeletal systems.
- No adverse effects on fetal growth and development occurred at 1 and 5 mg/kg/day, despite reductions in maternal body weight gain and food consumption at 5 mg/kg/day.
- The animal-to-human AUC ratio for EFD findings is approximately 0.7 times the human exposure at 150 mg once daily.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing: 1, 5, 20 mg/kg/day, daily dosing

Route of administration: oral gavage

Formulation/Vehicle (b) (4) ripretinib in HPMCAS (b) (4) methylcellulose (b) (4) in reverse osmosis water

Species/Strain: Sprague-Dawley rats

Number/Sex/Group: 24/f/group evaluated for toxicity

Satellite groups: 3/f group (one control group) and 6/f/group (3 groups) evaluated for TK parameters

Study design: Administration on gestation days (DG) 6 through 18

Deviation from study protocol affecting interpretation of results: No

Observations and Results

Parameters	Major findings
Mortality	None
Clinical Signs	No ripretinib-related clinical signs observed at any dose
Body Weights	Reduced maternal body weight gain occurred at 5 and 20 mg/kg/day during the overall treatment period, represented by measurement during DG 6-19. Concomitant reductions in food consumption occurred at these doses. No treatment-related effects on maternal body weight and food consumption were apparent at 1 mg/kg/day.
Necropsy findings Cesarean Section Data	1 mg/kg dose: No macroscopic findings 5 mg/kg dose: No macroscopic findings 20 mg/kg dose: No macroscopic findings
Necropsy findings Offspring	1 mg/kg dose: No effects 5 mg/kg dose: Bipartite thoracic centra observed. This delay in skeletal ossification was expected to resolve and was therefore considered non-adverse. 20 mg/kg dose: Reduced mean fetal weight, malformations associated with the cardiovascular and skeletal systems; increased incidence of absent digits; one fetus had multiple malformations that included malpositioned pinna, small head; absent eye bulge, mouth, and naris; and short digits on the forepaws.

Study title/ number: A Dose Range-Finding Embryofetal Development Study by Oral (Gavage) in Rabbits/Study DCC-2618-04-012

Key Study Findings

- DCC-2618-related abortions and maternal body weight loss were noted at 150 mg/kg/day, while clinical signs at ≥ 40 mg/kg/day, and lower body weight gain and food consumption at ≥ 2 mg/kg/day were observed, as well an increased post-implantation loss and reduced fetal body weights at 40 mg/kg/day
- All fetuses in the 2 and 10 mg/kg/day dose groups appeared grossly normal and no external abnormalities were observed in the 40 mg/kg/day dose group.
- Animal-to-human AUC ratio: 5.8 times the human exposure at 150 mg once daily.

Conducting laboratory and location: (b) (4)
GLP compliance: No

Methods

Dose and frequency of dosing: 2, 10, 40, and 150 mg/kg/day, daily dosing

Route of administration: oral gavage

Formulation/Vehicle (b) (4) ripretinib in HPMCAS (b) (4) methylcellulose (b) (4) in reverse osmosis water

Species/Strain: New Zealand White rabbits

Number/Sex/Group: 6/f/group evaluated for toxicity

Satellite groups: 3/f/group evaluated for TK

Study design: Administration on gestation days (DG) 7 through 19

Deviation from study protocol affecting interpretation of results: No

Observations and Results

Parameters	Major findings
Mortality	3 ripretinib-related abortions in the 150 mg/kg/day and were subsequently euthanized.
Clinical Signs	In 40 mg/kg/day abnormal fecal output (i.e., liquid or soft feces) between DG11 and DG 26. In 150 mg/kg/day suspected dehydration, thin appearance, ungroomed fur, abnormal breathing sounds, abnormal fecal output (i.e., decreased or soft feces), and red liquid material between DG 8 and DG 29.
Body Weights	Reduced mean maternal body weights occurred in the 150 mg/kg/day dose group beginning on DG 12 and continuing through DG 23 (90% to 72% of controls) and was associated with total litter loss in all pregnant females. Mean maternal body weights in the 2, 10, and 40mg/kg/day dose groups were comparable to the control group value throughout the treatment (DG 7 to 19) and post-treatment (DG 20 to 29) periods.
Necropsy findings Cesarean Section Data	2 mg/kg/day dose: No macroscopic findings 10 mg/kg/day dose: No macroscopic findings 40 mg/kg/day dose: No macroscopic findings 150 mg/kg/day dose: No macroscopic findings
Necropsy findings Offspring	2 mg/kg/day dose: No effects 10 mg/kg/day dose: No effects 40 mg/kg/day dose: No effects 150 mg/kg/day dose: No fetuses available for evaluation due to early embryonic death

Abbreviations: DG = Gestation days.

The Regulatory Authorities' Assessment:

The Regulatory Authorities agree with the summary of study results described above.

Additional study results are summarized below.

The Applicant conducted a dose-range finding study in rats (Study DCC-2618-04-0011) in which animals were dosed at 5, 20, 75, or 300 mg/kg daily. All dams survived to scheduled euthanasia and there were no gross macroscopic observations at any dose. Other findings were similar to those described in Study DCC-2618-04-0013, but total litter loss was observed at 75 and 300 mg/kg.

Study title/ number: Embryo-Fetal Development Study of ripretinib by Oral (Gavage) in Rats /Study DCC-2618-04-0013

In the 5 and 20 mg/kg/day dosing groups, mean maternal body weight gains were decreased (86% and 78% of controls) for the dosing interval (DG 6 to 19). The number of early resorptions and the percentage of postimplantation loss were increased at 20 mg/kg compared to controls, but this was primarily attributed to one female.

In the GLP-compliant definitive study, skeletal malformations observed at 20 mg/kg included malformed ribs (branched and fused), malformed vertebrae (absent caudal arch, absent cervical vertebrae, fused cervical arch, cervical or thoracic hemivertebrae, supernumerary cervical vertebrae, fused sacral centrum), absent forepaw phalanges and absent metacarpals (1 or 2 fetuses each). Additional malformations/variations observed included:

Malformations/variations	Incidence Fetuses N (%)	
Dose (mg/kg)	5	20
Total evaluated: Fetus (litter)	268 (24)	260 (23)
External		
Absent digits		6 (7.5)
Visceral		
Interrupted aortic arch		3 (5.6)
Retroesophageal aortic arch		4 (17.4)
Retroesophageal subclavian artery		3 (5.9)
Malpositioned carotid artery origin		2 (1.5)
Absent innominate artery		19 (18.3)
Elongated innominate artery		6 (4.3)
Malpositioned subclavian artery		6 (7.8)
Malpositioned subclavian artery origin		6 (7.8)
Skeletal		
Fused exoccipitals to first cervical vertebrae		9 (9.8)
Incompletely ossified sternal centra		3 (1.9)
Misshapen cervical arches		11 (10.8)
Bipartite ossified lumbar centra		6 (5)
Bipartite ossified thoracic centra	13 (8.6)	94 (71.9)
Unilaterally ossified thracic centra		15 (18.1)
Unossified thoracic centra		5 (3.2)

Source: Data summarized from Study DCC-2618-04-0013)

The animal-to-human AUC ratio for EFD findings in rats is approximately 0.4 times the human exposure at 150 mg once daily.

Study title/ number: A Dose Range-Finding Embryofetal Development Study by Oral (Gavage) in Rabbits/Study DCC-2618-04-012

40 mg/kg: Early resorptions were 2.8/litter compared with 0.2 (control group) and postimplantation loss was 28% as compared to 5% (control). In surviving fetuses, mean fetal body weights were decreased (84%, 83%, and 87% of controls, for male, female and combined, respectively).

150 mg/kg: total litter loss

The animal-to-human AUC ratio for EFD findings in rabbits is approximately 2.1 times the human exposure at 150 mg once daily.

5.5.5. Other Toxicology Studies

The phototoxicity and cytotoxicity potential of ripretinib was assessed by reduction in neutral red uptake in cultures of normal BALB/c 3T3 mouse fibroblasts. In the definitive assay, ripretinib demonstrated phototoxic potential with IC50 values of 0.842 and 1.361 µg/mL in the presence of UVR exposure, similar to 1.488 µg/mL observed for promethazine, the positive control. Ripretinib was not found to reduce viability of cells in the absence of UVR exposure. These results suggest that ripretinib exhibits the potential for UV-induced phototoxicity.

The Regulatory Authorities' Assessment:

The Regulatory Authorities agree that the results of the in vitro phototoxicity assay were positive.

A positive result in this test does not necessarily indicate a clinical phototoxicity risk; however, a positive in vitro result should trigger the initiation of an in vivo follow-up assessment per the ICH S10 Guidance for Industry: Photosafety Evaluation of Pharmaceuticals. Because an in vivo follow-up assessment was not conducted, and because no phototoxicity was observed in the INVICTUS Study, FDA disagrees with the Applicant's conclusion that ripretinib exhibits the potential for UV-induced phototoxicity.

X	X
Primary Reviewer	**Nonclinical Team Leader**
Elizabeth Spehalski	Matthew Thompson

6 Clinical Pharmacology

6.1. Executive Summary

The Regulatory Authorities' Assessment:

Ripretinib (QINLOCK) is a tyrosine kinase inhibitor of the KIT proto-oncogene receptor tyrosine kinase (KIT) and the platelet derived growth factor receptor α (PDGFRA). Ripretinib also inhibits secondary KIT and PDGFRA mutations. Its major metabolite, DP-5439 (M5) exhibits similar in vitro activity as ripretinib. The proposed dosage of QINLOCK is 150 mg orally once daily with or without food.

Study DCC-2618-03-001 supports FDA's assessment of the efficacy and safety of QINLOCK 150 mg once daily dosage regimen. Exploratory exposure-response (E-R) analyses for efficacy revealed that lower HR and longer PFS were associated with higher trough concentrations (C_{trough}) of combined ripretinib and DP-5439. No clinically meaningful E-R relationships were identified for safety including any grade and Grade 3 or higher hypertension, diarrhea, and hyperbilirubinemia. Ripretinib mean C_{trough} was numerically higher in patients with myalgia any grade and PPES any grade compared to patients without these AEs. No large change from baseline in the mean QT interval (i.e., > 20 ms) was observed in patients treated with ripretinib 150 mg once daily.

No clinically significant food effect on ripretinib absorption was observed, supporting administration of ripretinib with or without food. Ripretinib is primarily eliminated by hepatic metabolism with CYP3A4 as the major responsible enzyme. Ripretinib mean (%CV) half-life ($T_{1/2}$) following a single oral dose was 14.8 hours (30.3%). With daily dosing regimen, ripretinib steady state was achieved by Day 14, with 1.7-fold accumulation. Following single doses and at steady state, ripretinib exposures (AUC and C_{max}) were approximately dose proportional over the dose range of 20 to 150 mg. No dose adjustment for ripretinib is recommended for patients with mild hepatic impairment and for patients with mild or moderate renal impairments. Ripretinib has not been studied in patients with severe renal impairments and patients with moderate or severe hepatic impairment. Concomitant use of ripretinib with strong CYP3A inducers should be avoided. No dose adjustment is recommended for ripretinib when it is concomitantly used with a strong CYP3A inhibitor. Ripretinib and DP-5439 are inhibitors of CYP2C8.

US FDA Recommendations
The Office of Clinical Pharmacology has reviewed the information contained in the application and concludes that it is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below in Table 6.1.

Table 6.1. Key FDA Clinical Pharmacology Review Issues

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The efficacy of ripretinib in patients with GIST was demonstrated in a phase 3 randomized, double blind, placebo-controlled study DCC-2618-03-001. In addition, data from phase 1 study (Study DCC-2618-01-001) in patients with GIST support ripretinib efficacy.
General dosing instructions	The proposed dose of ripretinib of 150 mg orally once daily with or without food is supported by the following data: • This dosing regimen demonstrated a statistically significant PFS improvement in study DCC-2618-03-001 with a tolerable safety profile in patients with GIST. • In the phase 1 study (DCC-2618-01-001), 20-200 mg BID and 100-250 mg QD were studied and the MTD was not reached. • 150 mg once daily was predicted to maintain ripretinib exposure above the 10,000 ng·h/mL threshold for efficacy in > 90% of patients. • Exposure-response analyses demonstrated an association of longer PFS with higher combined ripretinib + DP-5439 C_{trough}. • A high-fat, high-calorie meal did not have a clinically significant effect on ripretinib exposure, supporting administration of ripretinib without regards to food intake.
Dosing in patient subgroups (intrinsic and extrinsic factors)	• No dose adjustment is recommended for patients with mild hepatic impairment and for patients with mild or moderate renal impairment. Ripretinib has not been studied in patients with moderate or severe hepatic impairment or in patients with severe renal impairment. • Avoid concomitant use of ripretinib with strong CYP3A inducers. • No dose adjustment is recommended for ripretinib when it is concomitantly used with a strong CYP3A inhibitor. • No dose adjustment is required based on age, weight, or sex.
Labeling	Proposed labeling is generally acceptable. The review team has recommendations on specific content and formatting changes. In addition, the Applicant's proposed labeling language has been modified according to the guidance of clinical pharmacology section of labeling for human prescription drug and biological products - content and format (published December 2016).
Bridge between the to-be-marketed and clinical trial formulations	Bioequivalence has been demonstrated between the to-be-marketed formulation and the clinical trial formulation of 50 mg ripretinib tablet.

Postmarketing Requirements (PMR) and Commitments (PMC)

The following PMRs and PMCs have been identified by the FDA clinical pharmacology review team:

- Hepatic impairment study (PMR)
- DDI study of ripretinib with CYP2C8 substrates (PMR)
- DDI study of ripretinib with a strong CYP3A inducer (rifampin) (PMC)
- PBPK modeling of ripretinib with a moderate CYP3A inducer (PMC)

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:

The clinical pharmacology of ripretinib and its active metabolite DP-5439 have been well characterized. The data in the dossier encompasses the pharmacokinetic properties following single dose and multiple-doses of ripretinib in both healthy subjects and subjects with advanced malignancies. In addition, a population pharmacokinetics (PK) analysis of data from the first in human study in patients with advanced malignancies and the Phase 3 study in fourth-line or greater GIST patients is included in the dossier. The results from both in vitro human biomaterial studies and in vivo clinical pharmacology studies in (food effect, proton pump inhibitor drug-drug interaction (DDI), CYP3A4 inhibitor DDI, relative bioavailability, and renal and fecal excretion with qualitative metabolite identification) were conducted. These data were integrated to describe the absorption, distribution, metabolism, excretion (ADME) properties of ripretinib in humans and assess intrinsic and extrinsic factors which may affect the PK of both ripretinib and DP-5439. In addition, exposure-efficacy and exposure-safety analyses were conducted to support the use of the recommended dose of 150 mg ripretinib, administered orally, once daily, on a continuous schedule.

The Regulatory Authorities' Assessment:

The Regulatory Authorities concur with the Applicant's assessment on clinical pharmacology and pharmacokinetics of ripretinib and its active metabolite DP-5439.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

The Applicant's Position:

Selection of the recommended Phase 2 dose (RP2D), ripretinib 150 mg daily continuous dosing schedule was based on the results of the first in-human study, DCC-2618-01-001. In Study DCC-2618-01-001, 237 patients with advanced malignancies enrolled in escalation and expansion phases and received at least 1 dose of ripretinib (data cut-off date of 1-Mar-2019). In the Escalation Phase, increasing doses of oral ripretinib (20-200 mg twice daily [BID] and 100-250 mg once daily [QD]) were evaluated pharmacologically and for dose limiting toxicities and maximum tolerated dose (MTD). Although MTD was not reached, the RP2D was determined to be 150 mg QD. The safety and efficacy of ripretinib 150 mg QD was further evaluated in the Phase 3 study DCC-2618-03-001 in the fourth line or greater setting in patients with GIST.

The clinical results of study DCC-2618-03-001 as well as the accompanying exposure-response analysis are in further support of the 150 mg QD dose in the target indication.

The Regulatory Authorities' Assessment:

The Regulatory Authorities concur with the Applicant's position that the proposed dosage regimen of ripretinib 150 mg orally once daily with or without food is supported by the established efficacy/safety data, results of the food effect study and exposure-response analyses. For more information, see section 6.3.2.

6.2.2.2. Therapeutic Individualization

The Applicant's Position:

No therapeutic individualization is needed in the proposed indication based on demographic factors (body weight, age, gender), DDIs that may affect ripretinib pharmacokinetics, or in special populations (mild hepatic or mild or moderate renal impairment). The pharmacokinetics and safety of ripretinib in patients with moderate or severe hepatic impairment or patients with severe renal impairment have not been studied. For more information, see Section 6.3.2.

The Regulatory Authorities' Assessment:

The Regulatory Authorities concurs with the Applicant's position that no dose adjustment is necessary based on demographic characteristics (body weight, age, sex) of the patients. Also, no dose adjustment is recommended for ripretinib in patients with mild hepatic impairment and in patients with mild or moderate renal impairment based on the population pharmacokinetics analysis. Results from phase 1 study (Study DCC-2618-01-003) and preclinical studies suggested that less than 1% of ripretinib and DP-5439 is eliminated unchanged in urine; therefore, a dedicated clinical study to assess the effect of renal impairment on exposures of ripretinib and DP-5439 is not necessary. A dedicated hepatic impairment study is currently ongoing and a PMR will be issued to submit the results of this study to provide ripretinib dosing recommendation in patients with moderate or severe hepatic impairment. FDA agrees with the Applicant that no dose adjustment is necessary when ripretinib is co-administered with strong CYP3A inhibitors. However, dosing recommendations for ripretinib when it is co-administered with a strong or moderate CYP3A inducer cannot be made due to lack of the data. PMCs will be issued to determine the appropriate dosing recommendations of ripretinib when it is co-administered with a strong or moderate CYP3A inducer. The clinical relevance of DDI is described in Section 6.3.2.4.

6.2.2.3. Outstanding Issues

The Applicant's Position:

There are no outstanding issues.

The FDA's Assessment:

The FDA agrees that there are no outstanding issues have been identified during the review of this application from a clinical pharmacology perspective, except that the following PMRs and PMCs have been identified:

- Hepatic impairment study (PMR)
- DDI study of ripretinib with CYP2C8 substrates (PMR)
- DDI study of ripretinib with a strong CYP3A inducer (rifampin) (PMC)
- PBPK modeling of ripretinib with a moderate CYP3A inducer (PMC)

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position:

An overview of the ADME properties, clinical pharmacokinetics, and DDI potential of ripretinib is provided below.

Absorption: Ripretinib is classified as a Class II/IV compound (low solubility, moderate permeability). The time to maximum observed concentration (t_{max}) of ripretinib after the administration of a single dose of ripretinib at 20 to 250 mg under fasted condition ranged from 2 to 10 hours. Following administration of ripretinib with a high-fat meal at the 150 mg dose, ripretinib area under the concentration-time curve from time 0 to 24 hours (AUC_{0-24}) and maximum observed concentration (C_{max}) were higher by 30% and 22%, respectively. DP-5439 AUC_{0-24} and C_{max} were higher by 47% and 66%, respectively.

Distribution: Both ripretinib and its active metabolite DP-5439 bind to plasma proteins at ≥ 99%. The apparent volume of distribution associated with the terminal phase (Vz/F) was 325 L in healthy subjects receiving a single 150 mg dose of ripretinib. The population PK model suggests an apparent volume of the central compartment of 20 L and an apparent volume of the peripheral compartment of 815 L. Ripretinib moderately partitions in blood cells with blood-to-plasma concentration ratios of 0.74 to 0.88.

Metabolism: The major metabolite observed in all species of hepatocytes is the N-desmethyl metabolite (ie, DP-5439). Exposure of the active metabolite, DP-5439, was approximately 49% of the parent ripretinib after single 150-mg doses and approximately 129% after 15 days of dosing at 150 mg QD. Cytochrome P450 (CYP) 3A4/5 is the major metabolizer of ripretinib, while CYP2C8 and CYP2D6 were implicated as only minor metabolizers. The major in vitro metabolism of DP-5439 was found to be CYP3A4/5 dependent, with metabolism also possible by CYP2C8, CYP2E1, and CYP2D6. Ripretinib was metabolized via oxidation, N-dealkylation, and glucuronidation. Ripretinib and its active metabolite DP-5439 were the most predominant components in plasma.

Elimination: Formulation challenges precluded the conduct of a human absorption, metabolism, and excretion study. Approximately 34% and 6% of the ripretinib dose was excreted in feces as the parent ripretinib and the major metabolite DP-5439, respectively, with <1% excreted in urine as the parent ripretinib and the major metabolite DP-5439, respectively. Dose Proportionality: Ripretinib single-dose PK parameters derived from noncompartmental analysis were generally dose proportional within the dose range of 20 to 150 mg, but less than dose proportional for C_{max} at higher doses of 200 and 250 mg.

Time Dependency: Steady-state conditions were achieved within 14 days.

Clinical Pharmacokinetics: Following single doses of ripretinib in the dose escalation phase of the DCC-2618-01-001 study in patients with advanced malignancies, the time to maximum observed concentration (t_{max}) ranged from 2 to 10 hours (Study DCC-2618-01-001). Ripretinib PK parameters were generally dose proportional within the dose range of 20 to 150 mg but appeared to be somewhat less than dose proportional for C_{max} at higher doses of 200 and 250 mg (Study DCC-2618-01-001). Geometric mean $t_{½}$ after single doses of ripretinib 50 mg and 150 mg in healthy subjects were 13.5 and 14.8 hours, respectively (Study DCC-2618-01-002). Following single doses, ripretinib pharmacokinetic parameters were highly variable, with CV% for C_{max} and AUC_{0-24} ranging from 33-61% at ripretinib doses 50-150 mg (Study DCC-2618-01-001). By Day 15, steady-state conditions for ripretinib were achieved.

Pharmacokinetics of the active metabolite, DP-5439, were generally similar to ripretinib, with plasma metabolite: parent ratio of 1.29 based on AUC_{0-t} (Study DCC-2618-01-001).

Victim DDI risk

CYP3A4 inhibitors: The strong CYP3A4/P-glycoprotein (P-gp, also known as multi-drug resistance-1 [MDR1]) inhibitor itraconazole at 200 mg QD increased ripretinib and DP-5439 AUCs by approximately 100%. Therefore, caution should be taken when taking ripretinib with strong CYP3A4 inhibitors.

Inhibition of transporters: Both ripretinib and DP-5439 are substrates for P-gp and breast cancer resistance protein (BCRP). Itraconazole increased ripretinib and DP-5439 AUCs by approximately 100%.

Gastric acid reducing agents: The proton pump inhibitor pantoprazole at 40 mg QD did not affect the PK exposure to ripretinib.

Effect of Ripretinib on Other Drugs

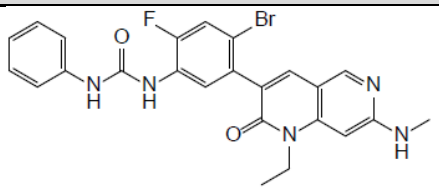
In vitro perpetrator DDI risk: The DDI potential of ripretinib and its primary metabolite DP-5439 was assessed in vitro with common metabolic enzymes and transporters. Ripretinib and DP-5439 did not appreciably inhibit CYP enzyme 3A4, CYP1A2, or CYP2B6 in in vitro metabolism studies. Ripretinib exhibited little or no evidence of time- or metabolism- dependent inhibition. Ripretinib may inhibit the metabolic clearance of co-medications metabolized by CYP2C8 based on a mechanistic model of drug interaction potential (for both ripretinib alone and in combination with DP-5439). Based on in vitro

induction studies, exhibits low risk for induction of hepatocyte CYP isoforms. In vitro studies suggested ripretinib is an inhibitor of P-gp and BCRP, and its metabolite DP-5439 is an inhibitor of BCRP and MATE1. The clinical relevance of these interactions is described in Section 6.3.2.4.

The Regulatory Authorities' Assessment:

The Regulatory Authorities generally agree with the Applicant's assessment of general clinical pharmacology and pharmacokinetic characteristics of ripretinib and DP-5439. The general overview of ripretinib and DP-5439 clinical pharmacology and pharmacokinetics information is presented in Table 6.2.

Table 6.2. The summary of ripretinib and DP-5439 clinical pharmacology and pharmacokinetics information

<table>
<tr><td colspan="2">Physicochemical characteristics</td></tr>
<tr><td>Chemical structure</td><td> 

Molecular formula: C24H21BrFN5O2
Molecular weight: 510.36 g/mol</td></tr>
<tr><td>Physical properties</td><td><u>Appearance:</u> Ripretinib is a white to off-white solid (b) (4) in crystalline form (b) (4).
<u>Solubility:</u> Ripretinib is a lipophilic (LogP 3.7), weak base compound (pKa 4.5), practically insoluble in aqueous media, exhibiting solubility of only 1.6 µg/mL in simulated gastric buffer (pH 2), and solubility of < 1 µg/mL in phosphate buffered saline (pH 6.5) in the presence or absence of up to 2% bile salts.</td></tr>
<tr><td colspan="2">Pharmacology</td></tr>
<tr><td>Mechanism of Action</td><td>Ripretinib is a tyrosine kinase inhibitor that inhibits KIT proto-oncogene receptor tyrosine kinase (KIT) and platelet derived growth factor receptor A (PDGFRA) kinase, including wild type, primary, and secondary mutations. Ripretinib also inhibits other kinases in vitro, such as PDGFRB, TIE2, VEGFR2, and BRAF.</td></tr>
<tr><td>Active Moieties</td><td>Ripretinib and its major metabolite DP-5439 (M5)</td></tr>
<tr><td>QT Prolongation</td><td>No large change from baseline in the mean QT interval (i.e. > 20 ms) was observed in patients treated with ripretinib.</td></tr>
<tr><td colspan="2">General Information</td></tr>
<tr><td>Bioanalysis</td><td>Plasma concentrations of ripretinib and its major metabolite DP-5439 in clinical studies were measured by validated LC-MS/MS. A summary of the method validation report is included in the Appendix 19.3.1.</td></tr>
<tr><td>Healthy volunteers vs. patients</td><td>A cross-study comparison suggests that pharmacokinetics of ripretinib and DP-5439 following 150 mg single dose of ripretinib are generally similar between GIST patients (Study DCC 2618-01-001) and healthy subjects (DCC 2618-01-002). AUC_{0-t} of ripretinib and DP-5439 appears higher in healthy subjects compared to that in cancer patients. However, these results should be interpreted with caution because the small number of healthy subjects were included in this analysis.
<table>
<tr><td></td><td colspan="3">Geometric Mean (CV%) PK Parameters of Ripretinib</td></tr>
<tr><td></td><td>AUC_{0-t} (ng•h/mL)</td><td>C_{max} (ng/mL)</td><td>T_{max} (h)</td></tr>
<tr><td>Healthy subjects (N=7)</td><td>9753 (43.5)</td><td>592 (31.3)</td><td>4 (3-8)</td></tr>
<tr><td>Cancer patients (N=24)</td><td>6634 (59.8)</td><td>502 (56.8)</td><td>4 (2-24)</td></tr>
<tr><td></td><td colspan="3">Geometric Mean (CV%) PK Parameters of DP-5439</td></tr>
<tr><td></td><td>AUC_{0-t} (ng•h/mL)</td><td>C_{max} (ng/mL)</td><td>T_{max} (h)</td></tr>
<tr><td>Healthy subjects (N=7)</td><td>7959 (55.2)</td><td>246 (33)</td><td>8 (4-24)</td></tr>
<tr><td>Cancer patients (N=22)</td><td>4096 (60.3)</td><td>231 (63.4)</td><td>15.6 (4-25)</td></tr>
</table></td></tr>
</table>

<table>
<tr><td>Drug exposure at steady state following the therapeutic dosing regimen</td><td>Ripretinib and DP-5439 steady state exposures following a once daily administration of 150 mg ripretinib in patients with advanced cancers including GIST.
<table>
<tr><th></th><th colspan="2">Geometric Mean (CV%) PK Parameters</th></tr>
<tr><th></th><th>$AUC_{0\text{-}t}$ (ng•h/mL)</th><th>C_{max} (ng/mL)</th></tr>
<tr><td>Ripretinib (N = 11)</td><td>5678 (32.1%)</td><td>761 (31.8%)</td></tr>
<tr><td>DP-5439 (N = 12)</td><td>7138 (44.4%)</td><td>804 (45.5%)</td></tr>
</table></td></tr>
<tr><td>Minimal effective dose or exposure</td><td>Based on preclinical studies, an exposure of combined ripretinib and DP-5439 of 10,000 ng·h/mL is required to achieve target inhibition in > 90% of patients.</td></tr>
<tr><td>Maximal tolerated dose or exposure</td><td>Ripretinib MTD was not reached. The maximum administered dose of ripretinib in patients with advanced malignancies was 200 mg twice daily.</td></tr>
<tr><td>Dose Proportionality</td><td>In patients with advanced malignancies, the exposures of ripretinib and DP-5439 were approximately dose proportional following oral administration at single or multiple doses over the dose range of 20-250 mg.
<table>
<tr><th rowspan="3">Power model analysis</th><th colspan="4">Slope (95% CI)</th></tr>
<tr><th colspan="2">Ripretinib</th><th colspan="2">DP-5439</th></tr>
<tr><th>$AUC_{0\text{-}12hr}$</th><th>C_{max}</th><th>$AUC_{0\text{-}12hr}$</th><th>C_{max}</th></tr>
<tr><td>Single dose
Day -7 and C1D1</td><td>0.87
(0.71, 1.02)</td><td>0.83
(0.68, 0.98)</td><td>0.97
(0.75, 1.18)</td><td>0.94
(0.72, 1.16)</td></tr>
<tr><td>Multiple once-daily dosing – C1D15</td><td>0.74
(0.07, 1.41)</td><td>0.6
(0.03, 1.16)</td><td>0.59
(-0.75, 1.9)</td><td>0.56
(-0.63, 1.75)</td></tr>
</table></td></tr>
<tr><td>Accumulation</td><td>Following a once daily administration of 150 mg in patients with advanced malignancies, a 1.7- and 5.3-fold accumulation for $AUC_{0\text{-}12h}$ was observed for ripretinib and DP-549, respectively.</td></tr>
<tr><td colspan="2">Absorption</td></tr>
<tr><td>Oral Bioavailability</td><td>Absolute oral bioavailability of ripretinib was not measured due to formulation challenges.</td></tr>
<tr><td>T_{max} [Oral]</td><td>Ripretinib T_{max} was 2 hrs (1, 8) and DP-5439 T_{max} was 6 hrs (1, 8) in cancer patients.</td></tr>
<tr><td>Food effect</td><td>Approximately 30% higher exposure of ripretinib and DP-5439 was observed when ripretinib (150 mg) was administered with a standardized high-fat, high-calorie meal compared with dosing at the fasted state.</td></tr>
<tr><td>Bioequivalent (BE) under Fasted Conditions</td><td>Ripretinib is supplied as 50 mg tablets for oral administration. The manufacturing process for the intended commercial formulation differs from that used during clinical development (b) (4) (b) (4) (b) (4). In vitro dissolution study showed comparative dissolution profiles. In vivo Study DCC-2618-01-002 in healthy subjects under fasted condition demonstrated bioequivalence between the to-be-market 50 mg ripretinib tablet and the clinical trial 50 mg ripretinib tablet.
<table>
<tr><th rowspan="2">PK Parameter</th><th colspan="2">Geometric LSM</th><th rowspan="2">% Ratio of LSM (Test / Reference)</th><th rowspan="2">90% CI</th><th rowspan="2">Equivalence of Test and Reference</th></tr>
<tr><th>Test[a] (n = 36)</th><th>Reference[b] (n = 70)</th></tr>
<tr><td>$AUC_{0\text{-}t}$ (ng•h/mL)</td><td>3631</td><td>3387</td><td>107.20</td><td>98.74, 116.39</td><td>Yes</td></tr>
<tr><td>$AUC_{0\text{-}\infty}$ (ng•h/mL)</td><td>3727</td><td>3493[c]</td><td>106.71</td><td>98.94, 115.08</td><td>Yes</td></tr>
<tr><td>C_{max} (ng/mL)</td><td>271</td><td>256</td><td>105.78</td><td>95.50, 117.16</td><td>Yes</td></tr>
</table></td></tr>
</table>

Distribution	
Volume of distribution	Ripretinib Vd = 307 L (38.6%), DP-5439 Vd = 507 L (50.5)
Plasma protein binding	>99% of ripretinib and DP-5439 bound to plasma proteins
Blood to plasma ratio	Ripretinib 0.74 to 0.88
Elimination	
Half-life ($T_{1/2}$)	Following a single 150 mg dose of ripretinib in healthy subjects, ripretinib $T_{1/2}$ was 14.8 hrs (30.3%) and DP-5439 $T_{1/2}$ was 17.8 hrs (23.3%). In patients, $T_{1/2}$ could not be determined due to once daily dosing schedule.
Metabolism	Ripretinib and DP-5439 are mainly metabolized via oxidation by CYP3A in the liver.
Clearance	Ripretinib has CL/F of 15.3 L/hr (45.2%) and DP-5439 has CL/F of 17.5 L/hr (72.7%). Systemic elimination is primarily in feces, with 34.2% and 5.9% of the ripretinib dose excreted in feces as the parent ripretinib and the major metabolite DP-5439, respectively. Only 0.02% and 0.1% of the ripretinib dose were excreted in urine as unchanged ripretinib and DP-5439, respectively.

6.3.2. Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:

Yes. Results from the Phase 3 exposure-efficacy analysis showed an exposure-efficacy relationship of combined average ripretinib + DP-5439 C_{min} up to the time of disease progression/death or censoring, with higher exposures associated with longer PFS. There were no exposure-safety relationships with ripretinib, DP-5439, or combined ripretinib + DP-5439 exposure, except for myalgia and palmar plantar erythrodysaesthesia syndrome (PPES). Ripretinib average C_{min} was higher in subjects with these adverse events (AEs) (any grade) compared to subjects without these AEs. As outlined in the clinical study protocols, adverse events such as PPES, arthralgia, myalgia, and hypertension can be managed through clinical interventions, dose interruptions and/or dose reductions (to 100 mg (b) (4) if toxicities cannot be managed by interruption and clinical intervention alone). Hence, ripretinib has a positive benefit-risk ratio in patients treated at a 150 mg daily dose regimen.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment that the exposure-response analyses of efficacy and safety support the effectiveness of the proposed ripretinib dosage regimen of 150 mg once daily. Caution should be exercised when interpreting the results of the exposure-efficacy analysis as it was based on a small sample size with one dosing regimen.

Findings from phase 1 study (Study DCC-2618-01-001) in patients with advanced malignancies including GIST provided the following additional supporting evidence:

a. In phase 1, DCC-2618-01-001 study, the MTD was not reached with doses of 20-200 mg BID and 100-250 mg QD and safety data support administration of 150 mg once daily as a tolerable dose.
b. In vivo pharmacology studies in xenograft mouse models indicated a target combined PK exposure of ripretinib and DP-5439, $AUC_{0\text{-}24hr}$ = 10,000 ng·h/mL, for tumor growth inhibition. A simulation conducted using the population PK model predicted that ripretinib at dose 150 mg once daily will maintain the combined PK exposure of ripretinib and DP-5439 above the presumed threshold for efficacy in > 90% of patients.

Analysis of data from the early clinical evaluation of ripretinib indicates that at dosage of 100 mg QD, ripretinib exposure is predicted to reach the exposure target for efficacy in 88% of patients. In the INVICTUS trial, 6 patients had dose reduction due to toxicity from 150 mg QD to 100 mg QD. While the clinical experience is limited at the 100 mg QD dosage, no evidence of decreased ripretinib efficacy was observed. Based on these observations and on the Applicant's proposal to re-escalate ripretinib as appropriate upon improvement or resolution of toxicity (a measure to help maintain ripretinib exposure at the optimal levels for its efficacy), FDA agrees with the Applicant's recommendation for dose reduction from 150 mg to 100 mg once daily.

FDA does not agree with the Applicant's proposed (b) (4)

(b) (4)

(b) (4)

Refer also to clinical reviewer assessment in Section 8 of this review.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The Applicant's Position:

Yes. The proposed dose of 150 mg daily is effective, manageable and generally well tolerated. Safety data from Study DCC-2618-03-001 were consistent with the ripretinib mechanism of action and the toxicity profile of the Phase 1 study. AEs were managed with concomitant medications, dose interruptions and/or reductions as needed. Details of AEs are provided in Section 8.2.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

The Applicant's Position:

No. Based on the assessment of intrinsic factors, no dose adjustment or change in regimen is required based on demographics or in special populations (i.e. mild hepatic and mild or moderate renal impairment). The effects or moderate and severe hepatic impairment and severe renal impairment are unknown.

Demographic Factors: Based on population analyses from Phase 1 (DCC-2618-01-001) and Phase 3 (DCC-2618-03-001) data, no clinically meaningful differences in ripretinib PK were observed based on age (19 to 87 years), sex, and race (White, Black, and Asian). As a result, there are no demographic characteristics that warrant dose adjustments.

Special Populations:

Hepatic impairment**:** No dose adjustment is necessary in subjects with mild hepatic impairment based on population PK analyses of data collected from studies in Phase 1 and Phase 3 patients with varying degrees of impairment based on National Cancer Institute Organ Dysfunction Working Group (NCI ODWG) criteria for hepatic dysfunction. The pharmacokinetics and safety of ripretinib in patients with moderate or severe hepatic impairment is unknown.

Renal impairment: No dose adjustment is necessary in subjects with mild or moderate renal impairment based upon the understanding of the fractional elimination pathway (i.e. negligible renal excretion and limited liver mediated metabolism) and further supported by the results of population PK analyses (Phase 1 and 3 analyses). The pharmacokinetics and safety of ripretinib in patients with severe renal impairment is unknown.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Based on the results of population PK analysis, no clinically significant differences in the PK of ripretinib and DP-5439 were observed based on age (19 to 87 years), sex, race (White, Black, and Asian), body weight (39 to 138 kg), tumor type (GIST or other solid tumor), prior gastrectomy, mild hepatic impairment (total bilirubin ≤1 x ULN and AST >1 x ULN or total bilirubin 1.0 to 1.5 x ULN, N = 89), mild (CLcr 60 to 89 ml/min, N = 93), moderate (CLcr 30 to 59 mL/min, N = 45) and severe (CLcr 15 to 29 mL/min, N=4) renal impairment. Limited data available to date do not allow definitive conclusions on KIT mutation subtypes and response.

Renal impairment: Results from a phase 1 study (Study DCC-2618-01-003) and preclinical studies suggested that less than 1% of ripretinib and DP-5439 is eliminated unchanged in urine; therefore, a dedicated clinical study to assess the effect of renal impairment on ripretinib and DP-5439 exposure is not required.

Hepatic impairment: Results from a phase 1 study (Study DCC-2618-01-003) and preclinical studies suggested that ripretinib and DP-5439 is eliminated mainly by hepatic metabolism. The effect of moderate and severe hepatic impairment on the PK of ripretinib and DP-5439 has not been evaluated. The Applicant is required to conduct a hepatic impairment study as a PMR.

KIT mutation-defined subgroups and response: FDA explored the association between KIT and PDGFRA mutation subtypes and treatment response in Studies DCC-2618-03-001 and DCC-2618-01-001. Responses (CR or PR) were not observed in patients with KIT exon 9 mutations. However, a small number of patients with exon 9 mutations were enrolled, and median PFS tended to be longer among KIT exon 9 mutation positive patients treated with ripretinib

compared to placebo, though less than in ripretinib-treated patients with exon 11 mutations (reviewer exploratory analysis). No responses were observed in patients with GIST negative for PDGFRA and KIT mutations suggesting that mutations in other genes may be driving tumor growth in this molecular subset. However, too few subjects are available to rule-out ripretinib response. See Appendix 19.3 for additional details.

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The Applicant's Position:

The effect of a high-fat breakfast was evaluated in the DCC-2618-01-001 study. Following administration of ripretinib with a high-fat meal at the 150 mg dose, ripretinib AUC_{0-24} and C_{max} were higher by 30% and 22%, respectively. For the metabolite DP-5439, AUC_{0-24} and C_{max} were higher by 47% and 66%, respectively. The food effect is not considered to be clinically significant based on exposure-response analysis. Therefore, ripretinib may be taken with or without food at approximately the same time each day.

The effects of CYP3A4 inhibition and gastric acid suppression on ripretinib PK were evaluated in the study DCC-2618-01-003 in stand-alone cohorts. Concomitant administration of itraconazole (a strong CYP3A4/P-gp inhibitor) 200 mg QD increased exposure to both ripretinib and its active metabolite DP-5439, by 94-99%, based on AUC. Although ripretinib has pH-dependent solubility, concomitant administration of a pantoprazole 40 mg QD did not affect ripretinb exposure.

Ripretinib may inhibit the metabolic clearance of co-medications metabolized by CYP2C8 based on a mechanistic model of in vitro drug interaction potential (for both ripretinib alone and in combination with DP-5439).

The FDA's Assessment:

The FDA generally concurs with the Applicant's assessment.

Food effect
The FDA agrees with the Applicant's assessment that the magnitude of food effect is not clinically significant. Patients in Study DCC-2618-03-001 received ripretinib without regard to food. The FDA however notes that the result of food effect analysis is confounded by the fasting conditions (administering ripretinib 1 hour before and at least 2 hours after a meal) that did not follow the FDA recommendation of drug administration after at least 10 hours fasting for a dedicated food effect study.

Table 6.3. Geometric LSMs, ratios, and 90% CIs of plasma pharmacokinetic parameters of ripretinib and DP-5439 following a single oral administration of 150 mg ripretinib under fed and fasted conditions in patients with advanced malignancies – Escalation Phase (Study DCC-2618-01-001)

	PK Parameter	Geometric LSM		% Ratio of LSM (Fed/Fasted)	90% CI
		Fasted (n = 12)	Fed (n = 12)		
Ripretinib	AUC0-12h (ng•h/mL)	4142	4734	114.3	94, 139
	AUC0-24h (ng•h/mL)	7183	9307	129.6	102, 164
	Cmax (ng/mL)	545	663	121.8	95, 157
DP-5439	AUC0-12h (ng•h/mL)	1780	1933	108.6	83, 142
	AUC0-24h (ng•h/mL)	4132	6091	147.4	112, 194
	Cmax (ng/mL)	233	386	166	123, 224

Drug-Drug interactions

In-vitro studies:

- Ripretinib and DP-5439 are substrates of CYP3A, P-gp and BCRP.
- Ripretinib and DP-5439 are not inducers of CYP enzymes.
- Ripretinib and DP-5439 are CYP2C8, CYP2C9, CYP2C19, and CYP2D6 inhibitors. Drug interaction risk assessment using the mechanistic model showed that only CYP2C8 activity could be inhibited by ripretinib and DP-5439 at clinically relevant plasma level.
- Ripretinib and DP-5439 are not inhibitors for most of the efflux and uptake transporters. Ripretinib inhibited P-gp and BCRP with IC50 values of 1.95 and 0.04 µM, respectively, and DP-5439 inhibited BCRP at an IC50 of 1.26 µM.
- Ripretinib (0.01 to 5 µM) did not appear to inhibit BCRP-mediated transport of DP-5439.

Clinical studies:

- Effect of other drugs on ripretinib

Strong CYP3A Inhibitors

Ripretinib and DP-5439 are metabolized by CYP3A; therefore, inhibitors and inducers of CYP3A could clinically affect exposures of ripretinib and DP-5439. Study DCC-2618-01-003 assessed the effect a strong CYP3A inhibitor (itraconazole) on the exposure of ripretinib and DP-5439. Inhibition of CYP3A by itraconazole increased the exposure of ripretinib and DP-5439 (Table

6.4).

Table 6.4. Geometric least-squares means, ratios, and 90% confidence intervals of plasma pharmacokinetic parameters of ripretinib and DP-5439 following a single oral administration of 50 mg ripretinib with or without itraconazole in healthy adult subjects - (Study DCC-2618-01-003)

	PK Parameter	Geometric LSM		% Ratio of LSM (Ripretinib + Itraconazole/ Ripretinib Alone)	90% CI
		Ripretinib Alone (n = 20)	Ripretinib + Itraconazole (n = 20)		
Ripretinib	AUC0-t (ng•h/mL)	4064	8060	198.4	173, 227
	AUC0-∞ (ng•h/mL)	4179	8305	198.7	174, 227
	Cmax (ng/mL)	291	395	135.7	116, 195
DP-5439	AUC0-24h (ng•h/mL)	3541	6884	194.4	167, 226
	AUC0-∞ (ng•h/mL)	3651	7277	199.4	171, 232
	Cmax (ng/mL)	114	121	106.3	91, 125

Increase in ripretinib and DP-5439 exposure due to CYP3A inhibition raises concerns on increasing the ripretinib toxicity. However, no dose adjustment is recommended based on demonstrated tolerable safety profile in ripretinib clinical studies. In Study DCC-2618-01-001, ripretinib was tolerated dosage regimens up to 200 mg BID and the MTD was not reached. In the phase 3 study, ripretinib was administered at 150 mg once daily in the double-blind period of the study and at 150 twice daily in the open-label period of the study. Comparing the exposure and safety of ripretinib between the double-blind period (150 mg QD) and open-label period (150 mg BID) showed that 2-fold increase in ripretinib exposure was not associated with additional safety concerns (Table 6.5 and 6.6). Finally, the exposure-response relationship for safety endpoints was flat except for a shallow exposure-response relationship with any grade myalgia and PPES. Therefore, the tolerable overall safety profile of ripretinib observed in the clinical trials with a low rate (14%-17%) of drug-related TEAE leading to dose interruption supports a “no dose adjustment” recommendation for ripretinib when it is co-administered with a strong CYP3A inhibitor; FDA recommends frequent monitoring patients for increased ripretinib toxicity when it is concomitantly used with strong CYP3A inhibitors.

Table 6.5. Ripretinib exposure following 150 mg once daily and twice daily dosing

Study	Ripretinib 150 mg QD			Ripretinib 150 mg BID		
	AUC_{0-t} (ng*h/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)	AUC_{0-t} (ng*h/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)
Phase 1 – Dose escalation	5678 (32%)	761 (32%)	284 (63%)	8614 (88.4%)	1290 (79%)	968 (114%)
Phase 3	N/A	N/A	352 (96%)	N/A	N/A	774 (78%)

Source: reviewer analysis of data from studies DCC-2618-01-001 and DCC-2618-03-001

Table 6.6. Ripretinib Safety following 150 mg once daily and twice daily dosing

Categories	Ripretinib 150 mg QD – Double blinded period (N = 85)	Ripretinib 150 mg BID – Open label period (N = 41)
Treatment duration (weeks)	24.4 (13.9)	14.8 (11.7)
Any drug-related TEAE	72 (84.7%)	29 (70.7%)
Any Grade 3/4 drug-related TEAE	21 (24.7%)	7 (17.1%)
Any drug-related SAE	8 (9.7%)	4 (9.8%)
Any drug-related TEAE leading to dose reduction	5 (5.9%)	1 (2.4%)
Any drug-related TEAE leading to dose interruption	12 (14.1%)	7 (17.1%)
Drug related TEAE ≥ 10%		
Myalgia	24 (28%)	5 (12%)
PPES	18 (21%)	5 (12%)

Source: reviewer analysis of data from studies DCC-2618-01-001 and DCC-2618-03-001

Strong CYP3A Inducers

The Applicant is planning to conduct a clinical study to assess the effect of a strong CYP3A inducer (rifampin) on the exposure of ripretinib and DP-5439. Accordingly, a PMC will be issued to submit the result of this study to support the dosing recommendation of ripretinib when it is co-administered with strong CYP3A inducer. Based on the results of this study, the need to evaluate the effect of moderate CYP inducer will be assessed. Until the results from the study assessing the exposure of ripretinib when it is co-administered with a strong inducer are available, FDA recommends that the concomitant use of strong CYP3A inducers with ripretinib be avoided, as reduced ripretinib exposure may substantially decrease its efficacy.

Gastric Acid Reducing Agents

The FDA agrees with the Applicant's proposal that no dose adjustment for ripretinib is recommended when it is co-administered with a gastric acid reducing agent. The results of the DCC-2618-01-003 study showed that the effect of the proton pump inhibitor pantoprazole at 40 mg once daily on the exposure of ripretinib is minimal and the magnitude of the effect on DP-5439 is not clinically meaningful (Table 6.7).

Table 6.7. Geometric least-squares means, ratios, and 90% confidence intervals of plasma pharmacokinetic parameters of ripretinib and DP-5439 following a single oral administration of 50 mg ripretinib with or without pantoprazole in healthy adult subjects - (Study DCC-2618-01-003)

	PK Parameter	Geometric LSM		% Ratio of LSM (Ripretinib + Pantoprazole/ Ripretinib Alone)	90% CI
		Ripretinib Alone (n = 23)	Ripretinib + Pantoprazole (n = 23)		
Ripretinib	AUC0-t (ng•h/mL)	3610	3935	109	97, 122
	AUC0-∞ (ng•h/mL)	3690	4034	109	97, 122
	Cmax (ng/mL)	289	298	103	91, 118
DP-5439	AUC0-24h (ng•h/mL)	2539	3325	131	111, 155
	AUC0-∞ (ng•h/mL)	2622	3412	130	110, 153
	Cmax (ng/mL)	109	122	112	96, 131

- Effect of ripretinib on other drugs

In vitro studies showed that ripretinib and DP-5439 could directly inhibit the activity of CYP2C8 at clinically relevant concentrations. The Applicant is planning to conduct a DDI study to assess the effect of ripretinib on the exposure of a CYP2C8 substrate. A PMR will be issued to submit the results of this study to support dosing recommendation for CYP2C8 substrates when it is co-administered with ripretinib.

X X

Primary Reviewer
Hisham Qosa
Youwei Bi
Jielin Sun

Team Leader
Hong Zhao
Jiang Liu
Rosane Charlab Orbach

7 Sources of Clinical Data

7.1. Table of Clinical Studies

The Applicant's Position:

All studies pertinent to the evaluation of efficacy and safety of ripretinib are summarized in Table 3.

Table 3: Clinical Trials Relevant to this NDA

Trial Identity, NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
DCC-2618-03-001 (INVICTUS), NCT03353753	Randomized, multicenter, double-blind, placebo-controlled	Ripretinib tablets; 150 mg QD or matching placebo[a]; Oral	Primary: PFS Based on independent radiologic review using modified RECIST Key Secondary: ORR Other secondary: OS, QOL, TTP based on IRR, time to response, and duration of response	Repeated 28-day cycles of treatment until progressive disease, experienced unacceptable toxicity, death, withdrawal of consent, lost to follow-up Ripretinib: mean (SD) treatment duration (24.44 [13.941] weeks)	129 patients enrolled (85 randomized to ripretinib and 44 randomized to placebo)	Patients with advanced GIST who had received treatment with prior anticancer therapies, which must have included imatinib, sunitinib, and regorafenib Age: ≥18 years	29 centers across 12 countries

Trial Identity, NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
				Placebo: mean (SD) treatment duration (8.25 [6.757] weeks)			
DCC-2618-01-001, NCT02571036	Open-label, multicenter, dose escalation and expansion, safety, PK/PD, and clinical activity study	Escalation Phase: Ripretinib tablet 20, 30, 50, 100, 150, 200 mg BID or 100, 150, 250 mg QD; Oral Expansion Phase: Ripretinib tablet 150 mg QD; Oral	Primary: safety and tolerability Escalation: MTD and recommended Phase 2 dose of oral ripretinib Expansion: antitumor activity of ripretinib in all diseases by ORR and DCR Secondary: PK Escalation: preliminary evidence of antitumor activity in patients with advanced malignancies by ORR and DCR	Escalation or Expansion Phase: Repeated 28-day cycles of treatment Until progressive disease, experienced unacceptable toxicity, death, withdrawal of consent, lost to follow-up	Escalation: 68 patients Expansion: 169 patients	Patients with advanced malignancies Age: ≥18 years	20 centers across 6 countries

Trial Identity, NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Clinical pharmacology studies							
DCC-2618-01-002	Open-label, randomized, single-dose, partial replicate, three-period, crossover	Ripretinib tablet; 50 mg (reference formulation); 50 mg (test formulation); Oral	Primary: C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ of ripretinib Secondary: safety and tolerability of ripretinib and active metabolite, DP-5439 and other PK measures of ripretinib such as $\%AUC_{extrap}$, t_{max}, CL/F, V_z/F, λz, $t_{1/2.}$ Other PK measures for metabolite: C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, t_{max}, t½, and the metabolite to parent ratio for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$	3 doses, 7 days apart[b]	50 subjects 40 subjects (dosed at 50 mg) 10 subjects (dosed at 150 mg)	Healthy subjects Age: 18-55 years	1 US site

Abbreviations: DCR = disease control rate; $AUC_{0-\infty}$ = area under the concentration-time curve to infinity; $\%AUC_{extrap}$ = percentage of AUC that is due to extrapolation from the last measurable concentration; CL/F = apparent systemic clearance; IRR = independent radiologic review; ORR = objective response rate; QOL = quality of life; TTP: time to tumor progression; V_z/F = apparent volume of distribution associated with the terminal phase; λz = first-order rate constant associated with the terminal (log-linear) portion of the concentration-time curve; $t_{1/2}$ = elimination half-life.

[a]Patients randomized to ripretinib 150 mg QD were given the option to continue ripretinib at an increased dose of 150 mg BID. Patients randomized to placebo who crossed over to receive ripretinib 150 mg QD and had disease progression by mRECIST based on Investigator assessment were given the option to continue ripretinib at an increased dose of 150 mg BID.

[b]For each cohort, the minimum washout period after the first dose of ripretinib was 7 days; the washout may have been extended to 14 days at Investigator's discretion.

The Regulatory Authorities' Assessment:

The clinical data for the Regulatory Authorities' assessment of the efficacy of ripretinib was primarily based upon the results of the DCC-2618-03-001 (INVICTUS) trial, which randomized 129 patients to receive single-agent ripretinib or placebo. Data from Study DCC-2618-01-001 provided supportive evidence of the anti-tumor activity of ripretinib in patients with advanced GIST.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

The efficacy data that support the marketing application is based primarily on the double-blind efficacy data available at the time of final analysis of registration study DCC-2618-03-001. Data from the Phase 1 Study DCC-2618-01-001 are used to support the efficacy evaluation.

8.1.1. DCC-2618-03-001 (INVICTUS Study)

The Applicant's Description:

Trial Design

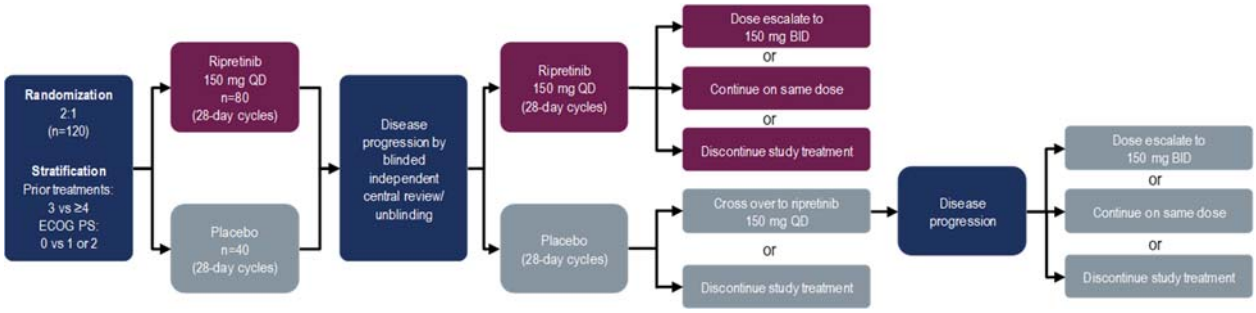
Basic design elements:

The pivotal study, DCC-2618-03-001 (INVICTUS), is a Phase 3, 2-arm, randomized, placebo-controlled, double-blind, international, multicenter study comparing the efficacy of ripretinib + best supportive care with placebo + best supportive care in patients with advanced GIST who have received prior anticancer treatment with imatinib, sunitinib, and regorafenib. Eligible study participants included those with histologic diagnosis of GIST and had progressive disease on imatinib, sunitinib, and regorafenib or had documented intolerance to any of these treatments despite dose modifications.

Approximately 120 patients (approximately 80 randomized to ripretinib and approximately 40 randomized to placebo) were planned to be enrolled in this study at approximately 35 centers globally.

An overview of study design is provided in Figure 1.

Figure 1: DCC-2618-03-001 Study Schematic[a, b]



[a]Blinded independent central review (also known as independent radiologic review).
[b]Following confirmation of disease progression, patients were unblinded and given the option to either cross over or dose escalate or continue on same dose of ripretinib, or discontinue from study treatment.

Trial location:

29 sites across 12 countries in North America, Europe, and Asia enrolled a total of 129 subjects.

Choice of control group:

Since no treatment is approved for the treatment of ≥ 4th line GIST, placebo was used as a comparator to treatment arm. The Applicant considered this the best option to adequately assess the benefit of ripretinib in this difficult to treat, highly heterogeneous patient population.

The Phase 3 study of ripretinib in ≥ 4th line GIST included a 2:1 randomization scheme of approximately 120 patients, which minimized the number of patients that received placebo. Treatment with best supportive care was allowed in both the active and placebo treatment arms.

Diagnostic criteria:

Histologic diagnosis of GIST.

Key Inclusion/Exclusion Criteria:

Enrollment was open to males and females ≥ 18 years of age that had a confirmed histologic diagnosis of GIST that have experienced disease progression or intolerance on imatinib, sunitinib, and regorafenib.

Subjects had at least 1 measurable lesion according to modified Response Evaluation Criteria in Solid Tumors (mRECIST) Version 1.1 (non-nodal lesions had ≥ 1.0 cm in the long axis or ≥ double the slide thickness in the long axis) within 21 days prior to the first dose of study drug.

Treatment with anticancer therapy, including investigational therapy, or investigational

procedures within 14 days or 5 x the half-life (whichever was longer) prior to the first dose of study drug was prohibited.

Dose selection:

Selection of the ripretinib 150 mg daily continuous dosing schedule was based on the results of the dose escalation part of Study DCC-2618-01-001 where ripretinib was administered at multiple doses and in vivo and in vitro pharmacology studies in an interim population PK analysis. Increased dose frequency from 150 mg QD to 150 mg BID was allowed in Study DCC-2618-03-001 based on supportive safety profile and predefined study criteria.

Study treatments, Assignment to Treatment, and Blinding:

Patients were randomized via an interactive response technology (IRT) system in a 2:1 ratio to receive either ripretinib 150 mg or placebo QD. Daily dosing was repeated in 28-day cycles and patients were instructed to take their assigned dose at the same time each day, with or without food.

Randomization was stratified by:

- Patients who had received 3 prior anticancer treatments versus patients who had received ≥ 4 prior anticancer treatments
- Eastern Cooperative Oncology Group (ECOG) = 0 versus ECOG = 1 or 2

All patients and site personnel, including the Investigator, the site monitor, and the study team participating in this study were blinded to treatment, with the exception of the following:

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

The Investigator, patient, site personnel, site monitor and specific study team members were unblinded to a patient's treatment assignment after the patient had disease progression based on independent radiologic review.

Dose modification/discontinuation:

Efficacy-related dosing changes

Patients randomized to placebo the arm who had disease progression as determined by mRECIST based on independent radiologic review (IRR) were given the option to cross over to receive ripretinib 150 mg QD. Once the IRR had confirmed disease progression, the patient's study drug treatment was unblinded as placebo, and either the patient started the crossover procedures, or discontinued, if the patient declined to enter the crossover.

After crossover, if disease progression on ripretinib was assessed by the Investigator based on mRECIST, patients could be given the option to continue ripretinib at the same dose, increase the dose to 150 mg BID, or discontinue treatment.

Safety-related dosing changes

Study drug could be interrupted or reduced at the discretion of the Investigator at any time due to AEs and according to the guidelines described in the Study Protocol. An interruption was limited to no more than 1 cycle (28 days). Upon resumption following a dose interruption, the Investigator would continue with the patient’s original visit schedule calculated from Cycle 1 Day 1.

Dose reduction occurred in reductions of 50 mg. If any patient required a dose lower than 50 mg QD or if a patient had their dose reduced and had disease progression confirmed by the independent radiologic reviewer, the patient was discontinued from study drug.

If a patient had 2 sequential dose reductions and the AE returned to Grade 1 or baseline at the second dose reduction level, the patient could be re-started at the first dose reduction level and kept at this dose level for 1 cycle without interruption before escalating to the starting dose level.

Administrative structure:

An IDMC monitored the safety data from this study on a periodic basis to help ensure the ongoing safety of study patients. The IDMC consisted of an experienced biostatistician and 2 qualified clinicians, who were not employees of the sponsor, with combined scientific expertise in general oncology and GIST as well as practical experience conducting clinical studies and monitoring safety and efficacy of clinical studies.

The IDMC or sponsor could request an ad hoc meeting for any reason, including significant unexpected safety event, unplanned unblinding of study results, follow-up of an observation during a planned IDMC meeting, or a report external to the study, such as publication of study results from a competing product.

The primary response for the study was evaluated using mRECIST Version 1.1 – GIST-specific based on independent radiologic review.

Procedures and schedule:

Patients were treated in 28-day cycles.

Efficacy was assessed by radiologic imaging every cycle through Cycle 4, then every other cycle during the blinded phase of the study (or if unblinded and found to be on ripretinib). If a patient crossed over, imaging was assessed every other cycle.

Safety assessments were completed during each cycle.

Treatment compliance:

All drug dosing occurred at the clinical site and was supervised by the Investigator or designee. At each study visit, site personnel reviewed that the patient was compliant with study drug dosing and reminded the patient of study drug dosing requirements. Compliance were also assessed by the Investigator by ongoing study drug count.

Subject completion, discontinuation, or withdrawal:

Subjects were to be treated until disease progression, unacceptable toxicity, withdrawal of consent, loss to follow-up, death, or discontinuation from the study treatment due to any other reason.

Subjects who withdrew from the study were not replaced, regardless of reason for withdrawal.

If a subject did not discontinue study treatment due to documented disease progression, death, lost to follow-up, or withdrawal of consent for efficacy follow-up, tumor and PRO assessments as well as overall survival assessments continued to be performed.

Study Endpoints

The study endpoints PFS, ORR, and OS are all accepted and well-recognized for oncology trials (FDA Guidance for Industry 2007).

The primary efficacy endpoint, progression-free survival (PFS), was defined and analyzed only for the double-blind period. PFS was defined as the interval between the date of randomization and the earliest documented evidence of the first disease progression (based on IRR assessment) or death due to any cause on initially assigned study treatment, whichever was earlier.

The key secondary endpoint for this study, objective response rate (ORR), was defined as the proportion of patients with a confirmed complete response (CR) or partial response (PR) based on IRR assessment during the initial assigned study treatment. To be assigned a status of a CR or PR, changes in tumor measurements must have been confirmed by repeat assessments that must have been performed at least 4 weeks (allowing a minus 3-day window) after the criteria for response were first met.

Historically, achieving a high Response Evaluation Criteria in Solid Tumors (RECIST)-confirmed ORR has been challenging in GIST in the post-imatinib setting, and stable disease is considered a clinically successful tumor response. Although not statistically significant, ripretinib achieved an ORR of 9.4% in this advanced study population with 7 of the 8 responders obtaining durable responses (median duration of response not yet reached). In addition, data from this study showed that ripretinib provided 37 weeks of added survival benefit over placebo.

Secondary efficacy analyses also included:

- Overall survival (OS) was defined as the interval between the date of randomization and date of death from any cause.
- Quality of life (QOL) as determined by changes from baseline in in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30 item (EORTC-QLQ-C30), EuroQol 5 Dimension 5 Level (EQ-5D-5L), and EQ-VAS
- Time to tumor progression (TTP) was defined as the interval between the date of randomization and the earliest documented evidence of first disease progression on initial treatment based on the IRR.
- Time to response (TTR) was defined as the interval between the date of randomization and the earliest date of first documented confirmed CR or earliest date of first documented confirmed PR if the patient did not have confirmed CR.
- Duration of response (DOR) was defined as the time interval from the first assessment of confirmed CR or PR until the first disease progression or death.

The Regulatory Authorities' Assessment:

The Regulatory Authorities agree with the summary of the study design.

The Applicant used modified RECIST v1.1 for GIST, wherein lymph nodes and bone lesions are not considered target lesions and a progressively growing new tumor nodule within a pre-existing tumor mass is required to meet specific criteria to be considered unequivocal evidence of progression. Patients with known active central nervous system metastases were excluded.

The FDA does not agree with the Applicant statement that there is 37 weeks added survival benefit in patients who were randomized to the ripretinib arm compared to those who were randomized to the placebo arm; inferences based on observed survival results should be interpreted with caution and are considered by FDA to be exploratory due to lack of allocation of alpha to test OS. A more appropriate comparison is that of the estimated median survival in each arm along with associated confidence intervals.

The FDA performed an analysis of dose reductions in the INVITUS trial, specifically from 150 mg QD to 100 mg QD (b) (4) This analysis was conducted to determine whether the Applicant's proposed dose reduction for toxicities were supported. The analysis focused on assessing duration at the reduced dose levels, whether patients were re-escalated, and the number of dose reductions and/or re-escalations per patient to determine if the dose reduction to 100 mg (b) (4) adversely impacted efficacy.

During the double-blind period, a total of seven patients experienced a dose reduction, six of them due to an AE). In these patients, duration of dose reductions ranged from 4 days to 148 days. Best overall response was partial response (n=1), stable disease (n=5), and disease progression (n=1). (b) (4) (b) (4); best response was stable disease. Three of the 7 patients were re-escalated back to 150 mg QD, and 2 others had multiple dose reductions and re-escalations.

Based on the limited data (b) (4), FDA is unable to assess whether patients receiving this dosage have the chance to experience the benefit of ripretinib. The FDA sent an Information Request to the Applicant on March 31, 2020, requesting information (b) (4) (b) (4). In the response dated April 3, 2020, the Applicant confirmed that (b) (4). The Applicant's justification for a dose reduction (b) (4) was that there may be some clinical benefit at this dose based on preclinical data, population PK (popPK) data, and exposure-response analysis though no definitive evidence existed to accurately estimate the efficacy threshold in patients. Refer to Section 6.3.2.1 "Does the clinical pharmacology program provide supportive evidence of effectiveness?" for the clinical pharmacology reviewer's assessment of the PK data.

The FDA considered the risks of decremental efficacy [redacted] (b) (4) in the context of the likelihood of dose reductions due to toxicity occurring in the post-approval setting, and the potential that these dose reductions may be of longer duration than observed in the limited clinical experience afforded by the INVICTUS trial. Ultimately, FDA concluded that there were insufficient data to support dose reductions below 100 mg QD.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The SAP was finalized prior to the conduct of any efficacy analysis and unblinding of the database.

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

Medical history and AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 21.1. Prior and concomitant medications and procedures were coded using the World Health Organization (WHO) Drug Dictionary (September 1, 2018) or higher.

One amendment was made to the SAP for this study. SAP version history for this study is below:

Statistical Analysis Plan – Final 1.0 (28 Nov 2018)
Statistical Analysis Plan – Final 2.0 (08 Aug 2019)

The Regulatory Authorities' Assessment:

The Regulatory Authorities agree with the Applicant's summary of the amendments to the SAP for study DCC-2618-03-001.

Protocol Amendments

The Applicant's Description:

The study protocol was amended five times during the study. None of the implemented changes impacted the integrity of the trial or the interpretation of the results. Key attributes of each amendment are provided in Table 4 .

Table 4: DCC-2618-03-001 Protocol Amendments

Amendment Number Date Final	Summary of Key Changes
Amendment 1 07 November 2017	Replaced TTP as key secondary objective with ORR. Clarified previous anticancer medications, specifically that patients must have received prior treatment with approved therapies, ie, with imatinib, sunitinib, and regorafenib, and that up to 40% of enrolled patients may have received prior treatment with imatinib, sunitinib, regorafenib, and other drugs (≥ 4 prior therapies) Updated to include number of events and sample size calculations by reducing the length of the study from 21 months to 15 months and increasing the dropout rate from 10% to 15%. Keratoacanthoma added as AESI. Updated the language of primary efficacy assessment as followed: Analysis for PFS will be un-stratified. The p-value will be from a 2-sided log-rank test at 0.05 significance level for evaluation of treatment difference. Point estimate of hazard ratio will be obtained from a Cox regression model and its 95% CI will be obtained using Wald method. Analysis will be using the mITT population as the primary analysis and PP as supportive. Added the following additional language for assessment of ORR: mITT population as the primary analysis and the PP population as supportive analysis; and unstratified 2-sided Fisher's Exact test at a 0.05 significance level will be used to investigate statistical differences between treatment arms. A 95% confidence interval of treatment rate difference in ORR will be calculated by the Wald method.
Amendment 2 01 March 2018	Allowed patients to dose-escalate mid-cycle. Increased contraceptive use and pregnancy reporting period to 104 days post final study drug exposure.
Amendment 3 22 March 2018	Modified to include patients with known KIT or PDGFRA wild-type GIST. Added additional information on medications to avoid or take with caution (ripretinib and DP-5439 exhibit potential for DDIs with other agents dependent on CYP2C8, CYP2C9, CYP2C19, or CYP2D6 for their metabolism).
Amendment 4 27 August 2018	Clarified inclusion criteria for adequate organ function and bone marrow reserve (#10) to include AST and ALT elevations (instead of AST or ALT elevations) and PT, INR and partial thromboplastin time (instead of PT, INR, or partial thromboplastin time). Added language regarding excluding patients with Stevens-Johnson Syndrome who had received prior treatment with TKI, based on data seen in the Phase 1 study (DCC-2618-01-001), and information about dose discontinuation for patients who experience Stevens-Johnson Syndrome.
Amendment 5 30 October 2018	Clarified the statistical analysis methodology, including: Clarified the analysis population definitions, including a global change of "mITT" to "ITT" Clarified the procedures for handling missing data

Amendment Number Date Final	Summary of Key Changes
	Clarified adjustments for multiplicity comparisons, including removing endpoints with low power and importance in the multiplicity testing procedure and clarified the QOL endpoints to be included in the testing procedure Clarified the conditions under which study unblinding may take place Clarified that the primary analysis would take place when 90 PFS events have occurred For the primary endpoint analysis (PFS) and the analysis of overall survival, changed the unstratified model to stratified model with stratification factors to comply to the ICH guidance.

Abbreviations: AESI = adverse event of special interest; ITT = intent-to-treat; mITT = modified intent-to-treat; PT = prothrombin time; INR = international normalized ratio; TKI = tyrosine kinase inhibitor.

The Regulatory Authorities' Assessment:

The Regulatory Authorities agree with the Applicant's summary of the protocol amendments for study DCC-2618-03-001.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant's Position:

This study was conducted in accordance with the consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines, the International Council on Harmonisation (ICH) Good Clinical Practices (GCP) Guideline [E6], and all applicable laws and regulations.

The Regulatory Authorities' Assessment:

The Regulatory Authorities confirm that a statement indicating that the DCC-2618-03-001 trial was conducted in accordance with the consensus ethics principles derived from international ethics guidelines, as stated above was submitted. The review uncovered no evidence that compliance with good clinical practices was violated during conduct of Study DCC-2618-03-001.

Financial Disclosure

The Applicant's Position:

Details of financial disclosure are provided in Section 19.2.

The Regulatory Authorities' Assessment:

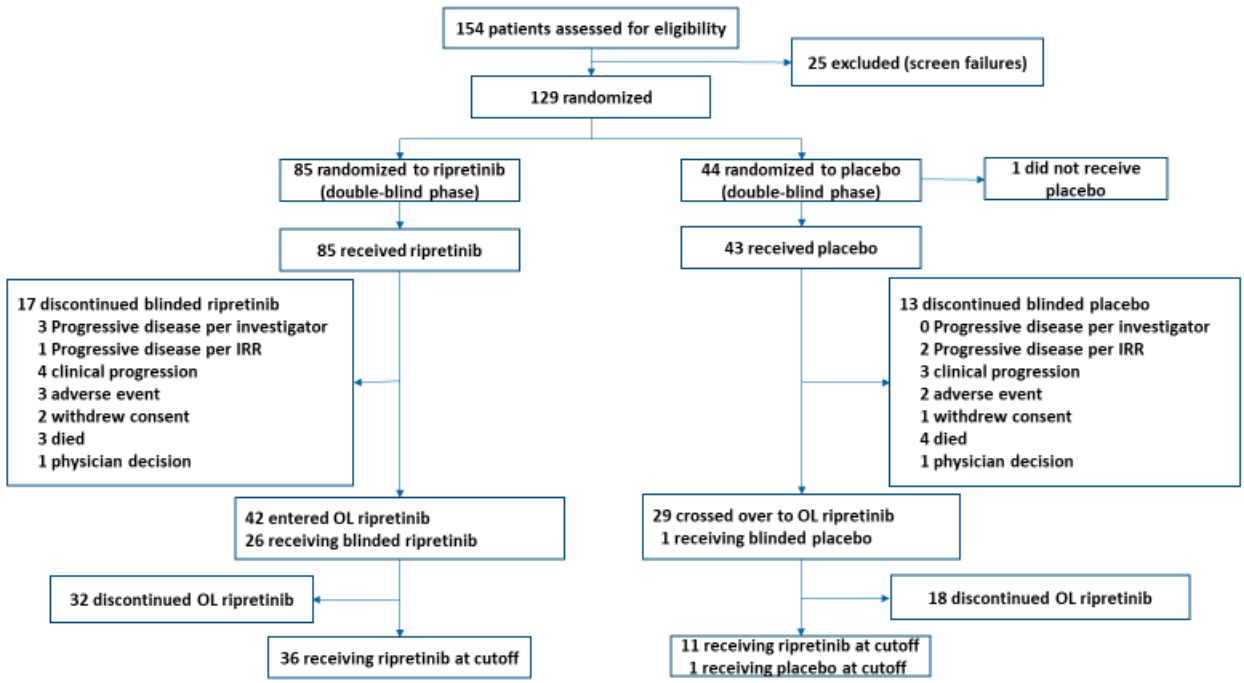
Refer to Regulatory Authorities' assessment in Section 19.2.

Patient Disposition

The Applicant's Position:

Overall patient disposition for Study DCC-2618-03-001 is presented in Figure 2. Results provided herein focus on the double-blind period of the study.

Figure 2: Study DCC-2618-03-001: Patient Disposition by Double-blind and Open-label Periods



Abbreviations: OL = open-label; IRR = independent radiologic review.
Data cutoff date: 31 May 2019.

Table 5 presents the patient disposition for the double-blind period. Of the 154 patients screened, 25 patients failed to meet the eligibility criteria and were not randomized to a study treatment.

As of 31 May 2019, 129 patients had been enrolled in the double-blind period in the ITT population. In the ITT/PP population, patient arms were based on the treatment initially assigned; in the safety/PK population, patient arms were based on the treatment initially received, resulting in differences in numbers in the different populations. One patient was randomized to placebo but was never treated, and therefore was not included in the safety population; the remaining patients in the safety population (N = 128) were treated with originally assigned treatment.

Of the 129 patients enrolled in the double-blind period (ITT population), 85 patients were randomized to the ripretinib arm and 44 patients were randomized to the placebo arm.

Overall 30 (23.4%) of 129 patients in the ITT population discontinued study treatment during the double-blind period. The most common reasons for treatment discontinuation were clinical progression, death (7 [5.5%] patients each) and AE (5 [3.9%] patients). Additional reasons for treatment discontinuation are presented in Table 5.

By treatment arm, 17 (20.0%) patients in the ripretinib arm and 13 (30.2%) patients in the placebo arm discontinued treatment during the double-blind period. Clinical progression was the most common reason for treatment discontinuation in the ripretinib arm (4 [4.7%] patients), and death was the most common reason for discontinuation of treatment for the placebo arm (4 [9.3%] patients). In the placebo arm, 2 (4.7%) patients discontinued treatment due to an AE vs 3 (3.5%) patients discontinuing treatment due to an AE in the ripretinib arm in the double-blind period. There were 71 (55.5%) patients that had disease progression and entered the open-label period, including 42 (49.4%) patients in the ripretinib arm and 29 (67.4%) patients in the placebo arm.

A total of 29 (22.5%) of the 129 patients in the ITT population discontinued the study during double-blind period; the most common reason for study discontinuation was death (25 [19.4%] patients) and 4 (3.1%) patients withdrew consent.

By treatment arm, 15 (17.6 %) patients in the ripretinib arm and 14 (31.8%) patients in the placebo arm discontinued the study. Death was the most common reason for study discontinuation in both treatment arms: 12 (14.1%) patients in the ripretinib arm and 13 (29.5%) patients in the placebo arm.

A total of 27 (21.1%) of the 129 patients in the ITT population remained on their blinded treatment in the double-blind period at the data cutoff date with 26 (30.6%) patients in the ripretinib arm and 1 (2.3%) patient in the placebo arm.

Table 5: Study DCC-2618-03-001: Patient Disposition- Double-blind Period (ITT Population)

	Placebo (N = 44) n (%)	Ripretinib (N = 85) n (%)	Total (N = 129) n (%)
Populations			
ITT Population	44 (100.0)	85 (100.0)	129 (100.0)
Safety Population	43 (97.7)	85 (100.0)	128 (99.2)
PP Population	42 (95.5)	81 (95.3)	123 (95.3)
PK Population	28 (63.6)	85 (100.0)	113 (87.6)
Entered Open-label Period [1]	29 (67.4)	42 (49.4)	71 (55.5)
Ongoing [1]	1 (2.3)	26 (30.6)	27 (21.1)
Discontinued Treatment [1]	13 (30.2)	17 (20.0)	30 (23.4)
Primary Reason for Treatment Discontinuation [1]			
Adverse Event	2 (4.7)	3 (3.5)	5 (3.9)
Clinical Progression	3 (7.0)	4 (4.7)	7 (5.5)
Death	4 (9.3)	3 (3.5)	7 (5.5)
Physician Decision	1 (2.3)	1 (1.2)	2 (1.6)
Confirmed Progressive Disease by Investigator Assessment	0	3 (3.5)	3 (2.3)
Confirmed Progressive Disease by Independent Radiologic Review	2 (4.7)	1 (1.2)	3 (2.3)
Withdrawal of Consent from Study	0	2 (2.4)	2 (1.6)
Withdrawal of Consent from Treatment	1 (2.3)	0	1 (0.8)
Discontinued Study [2]	14 (31.8)	15 (17.6)	29 (22.5)
Primary Reason for Study Discontinuation [2]			
Death	13 (29.5)	12 (14.1)	25 (19.4)
Withdrawal of Consent from Study	1 (2.3)	3 (3.5)	4 (3.1)

Abbreviations: ITT = intention-to-treat; PP = per protocol; PK = pharmacokinetics.
[1] Denominators are based on number of patients in the safety population.
[2] Denominators for study discontinuation are based on number of patients in the ITT population.
Note 1: In the ITT/PP population, patient groups are based on the treatment initially assigned; in the safety/PK population, patient groups are based on the treatment initially received.
Note 2: The ITT population is defined as all patients who signed the informed consent and were randomized. The safety population is defined as all patients who have received at least 1 dose of study drug. One patient was randomized to placebo but was never treated; the rest of the patients in the ITT population (N = 128) were treated by their originally assigned treatment. The PP population is defined as randomized patients who do not

have important protocol deviations that are expected to compromise the efficacy and/or safety assessments, including inclusion/exclusion criteria deviations, patient receiving wrong treatment, patient receiving incorrect dose, and patient receiving prohibited medications. The PK population is defined as all patients who received at least 1 dose of ripretinib and had at least 1 nonmissing PK concentration in plasma reported for ripretinib or active metabolite, DP-5439.

The Regulatory Authorities' Assessment:

The Regulatory Authorities agree with the Applicant's assessment of patient disposition.

Protocol Violations/Deviations

The Applicant's Position:

Important protocol deviations during the double-blind period are presented in Table 6. Six patients (2 randomized to placebo and 4 to ripretinib) had important protocol deviations and were excluded from the PP population. The overall nature of protocol deviations do not alter the conclusion of a net favorable benefit-risk relationship.

Table 6: Study DCC-2618-03-001: Important Protocol Deviations During Double-blind Period (ITT Population, All Sites)

Deviation	Placebo (N = 44) n (%)	Ripretinib (N = 85) n (%)	Total (N = 129) n (%)
Any Important Deviations	2 (4.5)	4 (4.7)	6 (4.7)
Patient did not satisfy entry criteria	1 (2.3)	2 (2.4)	3 (2.3)
Patient received incorrect dose	1 (2.3)	1 (1.2)	2 (1.6)
Patient received prohibited medication	1 (2.3)	1 (1.2)	2 (1.6)

Abbreviations: ITT = intention-to-treat.
Note: Patient groups are based on the treatment initially assigned.
Source: DCC-2618-03-001 CSR, Table 14.1.2

The Regulatory Authorities' Assessment:

The Regulatory Authorities agree with the Applicant's analysis for major protocol violations/deviations. Major protocol violations were low in frequency and no patients were removed from the analysis due to a protocol deviation.

Demographic and Baseline Characteristics

The Applicant's Position:

Overall, demographics and baseline characteristics were generally well balanced across both treatment arms (Table 7). The placebo arm had a higher percentage of patients aged ≥ 75 years old (22.7% vs 9.4% in the ripretinib arm), a higher percentage of Asian patients (11.4% vs 4.7% in the ripretinib arm) and a lower percentage of Black or African American patients (4.5% vs 9.4% in the ripretinib arm). The ripretinib arm had a higher percentage of patients aged 18-64 years old (57 (67.1%) vs 22 (50.0%) in the placebo arm). Note that stratification factors included ECOG status and the number of prior systemic anticancer treatments.

Table 7: Study DCC-2618-03-001: Demographic and Baseline Characteristics in Double-blind Period (ITT Population)

	Statistics	Placebo (N = 44)	Ripretinib (N = 85)	Total (N = 129)
Gender				
Female	n (%)	18 (40.9)	38 (44.7)	56 (43.4)
Male	n (%)	26 (59.1)	47 (55.3)	73 (56.6)
Age at Informed Consent (years) [1]	n	44	85	129
	Mean (SD)	62.0 (13.50)	59.1 (10.84)	60.1 (11.84)
	Median	64.5	59.0	60.0
	Min, Max	33, 83	29, 82	29, 83
Age Category (years)				
18 - 64 Years	n (%)	22 (50.0)	57 (67.1)	79 (61.2)
65 - 74 Years	n (%)	12 (27.3)	20 (23.5)	32 (24.8)
75 Years or Older	n (%)	10 (22.7)	8 (9.4)	18 (14.0)
Race				
Asian	n (%)	5 (11.4)	4 (4.7)	9 (7.0)
Black or African American	n (%)	2 (4.5)	8 (9.4)	10 (7.8)
White	n (%)	33 (75.0)	64 (75.3)	97 (75.2)
Not Reported	n (%)	4 (9.1)	8 (9.4)	12 (9.3)
Other	n (%)	0	1 (1.2)	1 (0.8)

	Statistics	Placebo (N = 44)	Ripretinib (N = 85)	Total (N = 129)
Race Category				
White	n (%)	33 (75.0)	64 (75.3)	97 (75.2)
Non-white	n (%)	7 (15.9)	13 (15.3)	20 (15.5)
Not Reported	n (%)	4 (9.1)	8 (9.4)	12 (9.3)
Ethnicity				
Hispanic or Latino	n (%)	0	1 (1.2)	1 (0.8)
Not Hispanic or Latino	n (%)	38 (86.4)	76 (89.4)	114 (88.4)
Not Reported	n (%)	5 (11.4)	5 (5.9)	10 (7.8)
Unknown	n (%)	1 (2.3)	3 (3.5)	4 (3.1)
Region [2]				
US	n (%)	20 (45.5)	40 (47.1)	60 (46.5)
Non-US	n (%)	24 (54.5)	45 (52.9)	69 (53.5)
Height (cm)	n	42	84	126
	Mean (SD)	169.7 (11.72)	169.7 (10.38)	169.7 (10.80)
	Median	170.0	169.3	170.0
	Min, Max	151, 190	147, 192	147, 192
Weight (kg)	n	43	85	128
	Mean (SD)	71.4 (18.04)	73.9 (19.02)	73.1 (18.67)
	Median	67.5	73.0	70.6
	Min, Max	44, 110	39, 133	39, 133
BMI (kg/m^2) [3]	n	42	84	126
	Mean (SD)	24.5 (5.08)	25.6 (6.22)	25.3 (5.87)
	Median	22.9	24.4	23.5
	Min, Max	16, 39	13, 47	13, 47
ECOG Score at Screening [4]				
0	n (%)	17 (38.6)	37 (43.5)	54 (41.9)
1	n (%)	24 (54.5)	40 (47.1)	64 (49.6)
2	n (%)	3 (6.8)	8 (9.4)	11 (8.5)

	Statistics	Placebo (N = 44)	Ripretinib (N = 85)	Total (N = 129)
ECOG Stratum at Screening [5]				
0	n (%)	19 (43.2)	38 (44.7)	57 (44.2)
1 or 2	n (%)	25 (56.8)	47 (55.3)	72 (55.8)
Number of Prior Systemic Anticancer Treatments [6]				
3	n (%)	27 (61.4)	54 (63.5)	81 (62.8)
≥ 4	n (%)	17 (38.6)	31 (36.5)	48 (37.2)

Abbreviations: BMI = body mass index; ECOG = Eastern Cooperative Oncology Group performance status, ITT = intention-to-treat; IRT = interactive response technology; UK = United Kingdom; US = United States.
[1] Age at Informed Consent is calculated as (date of informed consent - date of birth+1)/365.25 if not collected on the case report form. [2] Non-US countries include Canada, Australia, Belgium, UK, France, Germany, Italy, Netherlands, Poland, Singapore, Spain. [3] BMI = weight[kg]/height[m]^2. [4] ECOG Score at Screening was collected on the case report form. [5] ECOG Stratum at Screening in IRT was used for randomization stratification.
[6] Stratum by number of prior systemic anticancer treatments for randomization stratification.
Note: Patient groups are based on the treatment initially assigned.
The "Other" race category includes 1 patient whose race is "Indian".
Source: DCC-2618-03-001 CSR, Table 17

The Regulatory Authorities' Assessment:

The Regulatory Authorities agree with the Applicant's presentation of the demographic and baseline characteristics of patients enrolled in the INVICTUS trial. Most notably, there were more patients aged 18-64 years in the ripretinib arm (67% versus 50% in the placebo arm) and more patients ≥75 years in the placebo arm (23% versus 9% in the placebo arm; more Asians in the placebo arm (11% versus 5% in the ripretinib arm). The results of subgroup analysis for efficacy were included in the NDA submission to determine whether these differences affected outcome. Refer to Section 8.1.6 subheading Subpopulations.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs

The Applicant's Position:

Cancer history for the ITT population is summarized in Table 8.

Table 8: Study DCC-2618-03-001: Cancer History (ITT Population)

Categories	Statistics	Placebo (N = 44)	Ripretinib (N = 85)	Total (N = 129)
Site of Primary Tumor				
Gastric	n (%)	18 (40.9)	40 (47.1)	58 (45.0)
Duodenum	n (%)	8 (18.2)	2 (2.4)	10 (7.8)
Jejunum/Ileum	n (%)	8 (18.2)	20 (23.5)	28 (21.7)
Colon/Rectum	n (%)	0	9 (10.6)	9 (7.0)
Mesenteric/Omental	n (%)	6 (13.6)	6 (7.1)	12 (9.3)
Other	n (%)	4 (9.1)	7 (8.2)	11 (8.5)
Unknown	n (%)	0	1 (1.2)	1 (0.8)
Tumor Mutation Gene				
KIT Exon 9	n (%)	6 (13.6)	14 (16.5)	20 (15.5)
KIT Exon 11	n (%)	28 (63.6)	47 (55.3)	75 (58.1)
KIT Other Exons	n (%)	2 (4.5)	2 (2.4)	4 (3.1)
PDGFRA	n (%)	0	3 (3.5)	3 (2.3)
KIT wt / PDGFRA wt	n (%)	3 (6.8)	7 (8.2)	10 (7.8)
Not Available	n (%)	5 (11.4)	11 (12.9)	16 (12.4)
Not Done	n (%)	0	1 (1.2)	1 (0.8)
Stage at Initial Diagnosis				
Stage I	n (%)	0	2 (2.4)	2 (1.6)
Stage IA	n (%)	1 (2.3)	1 (1.2)	2 (1.6)
Stage IB	n (%)	0	2 (2.4)	2 (1.6)
Stage II	n (%)	1 (2.3)	1 (1.2)	2 (1.6)
Stage IIIA	n (%)	0	7 (8.2)	7 (5.4)
Stage IIIB	n (%)	6 (13.6)	7 (8.2)	13 (10.1)
Stage IV	n (%)	30 (68.2)	56 (65.9)	86 (66.7)

Categories	Statistics	Placebo (N = 44)	Ripretinib (N = 85)	Total (N = 129)
Unknown	n (%)	6 (13.6)	9 (10.6)	15 (11.6)
Histology at Initial Diagnosis				
Epithelioid	n (%)	3 (6.8)	17 (20.0)	20 (15.5)
Mixed Spindle Cell and Epithelioid	n (%)	4 (9.1)	16 (18.8)	20 (15.5)
Spindle Cell	n (%)	31 (70.5)	37 (43.5)	68 (52.7)
Other	n (%)	4 (9.1)	10 (11.8)	14 (10.9)
Unknown	n (%)	2 (4.5)	5 (5.9)	7 (5.4)
Time Since Initial Diagnosis (Years) [1]	n	44	85	129
	Mean (SD)	7.16 (4.328)	7.11 (4.129)	7.13 (4.181)
	Median	5.42	5.87	5.69
	Min, Max	1.4, 17.5	1.5, 16.4	1.4, 17.5

Abbreviations: ITT = intention-to-treat; KIT = CD117, a receptor tyrosine kinase that normally resides at the cell surface; PDGFRA = platelet derived growth factor receptor alpha; wt = wild type.
[1] Time since initial diagnosis calculated as (Informed Consent Date – Date of Initial Diagnosis+1)/365.25.
Note: Patient groups are based on the treatment initially assigned.
Source: DCC-2618-03-001 CSR, Table 14.1.5.1

The Regulatory Authorities' Assessment:

The Regulatory Authorities agree with the Applicant's assessment of other baseline characteristics, as presented above. The distribution of baseline characteristics as reported in study DCC-2618-03-001 appear consistent with what is reported in the literature in patients with advanced GIST. The most common site for GIST tumors is the stomach with the spindle cell type being the most common histologic subtype (Jumniensuk, et al 2018). KIT exon 11 mutations are the most common mutation followed by KIT exon 9 mutations (Subramanian et al 2004).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

Treatment Compliance

Treatment compliance was monitored by all used, partially used, and full study drug bottles returned to the site. To measure the compliance to the study drug, compliance (%) was calculated as (total number of days dosed)/(treatment duration in days) x 100. For the

double-blind period, compliance ≥ 80% was seen in 84 (98.8%) patients in the ripretinib arm and 36 (83.7%) patients in the placebo arm.

Relative dose intensity (%) = total dose (mg) / total planned dose (mg) x 100. Median relative dose intensity was 100% in the ripretinib arm, and 97.0% in the placebo arm.

Patients could receive a reduced dose or temporary dose interruption to manage AEs according to the dose modification guidelines in the protocol. Any dose modification occurred in 21 (24.7%) patients in the ripretinib arm and 9 (20.9%) patients in the placebo arm. The most frequent dose modification was due to dose interruption: 18 (21.2%) patients in the ripretinib arm and 8 (18.6%) patients in the placebo arm. Dose reductions were made in 7 (8.2%) patients in the ripretinib arm and 1 (2.3%) patient in the placebo arm.

Dose increases occurred when returning to the prior dose after a dose reduction (eg, dose increase to 150 mg QD after dose reduction to 100 mg QD). Dose increases were made in 3 (3.5%) patients in ripretinib arm (dose increase does not include dose escalation of ripretinib to 150 mg BID).

Concomitant Medications

All 128 (100%) patients in the safety population received at least 1 concomitant medication. The most frequently used medications (≥ 15% of patients) by preferred name included paracetamol (62 [48.4%] patients), oxycodone (30 [23.4%] patients), ranitidine (29 [22.7%] patients), furosemide (25 [19.5%] patients), urea (24 [18.8%] patients), lorazepam and ibuprofen (23 [18.0%] patients each), amlodipine (22 [17.2%] patients), levothyroxine sodium (22 [17.2%] patients), and ondansetron hydrochloride (21 [16.4%] patients).

Rescue Medication

Not applicable.

The Regulatory Authorities' Assessment:

The Regulatory Authorities generally agree with the Applicant's assessment above. The reported incidence of dose reductions or temporary dose interruption appears to be based on exposure records in patients who received at least one dose of study drug (safety set). FDA is able to confirm the numbers reported based on the analysis ADEX dataset. The results of the analyses of dose interruptions and dose reductions based on adverse event reporting is included in Section 8.2.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

The Applicant's Position:

PFS was defined as the interval between the date of randomization and the earliest documented evidence of disease progression based on the IRR, or death due to any cause on initially assigned study treatment, whichever comes earlier. Of the 85 patients in the ripretinib arm, 51 (60%) patients had PFS events and 34 (40%) patients were censored. Of the 44 patients in the placebo arm, 37 (84.1%) had PFS events and 7 (15.9%) patients were censored.
The median (95% CI) PFS was 27.6 (20.0, 29.9) weeks for the ripretinib arm and 4.1 (4.0, 7.3) weeks for the placebo arm. Patients in the ripretinib arm had an 85% reduced risk of disease progression or death which was statistically significant (hazard ratio = 0.15; stratified log-rank test $p < 0.0001$) compared to placebo. Since the number of PFS events included in the primary analysis (88 events) was less than the planned 90 events, an O'Brien-Fleming method was considered to assess the robustness of the result. Using the O'Brien-Fleming method, the alpha level was adjusted to be 0.047 and the hypothesis test of PFS ($p<0.0001$) still remained highly statistically significant at the adjusted alpha level.

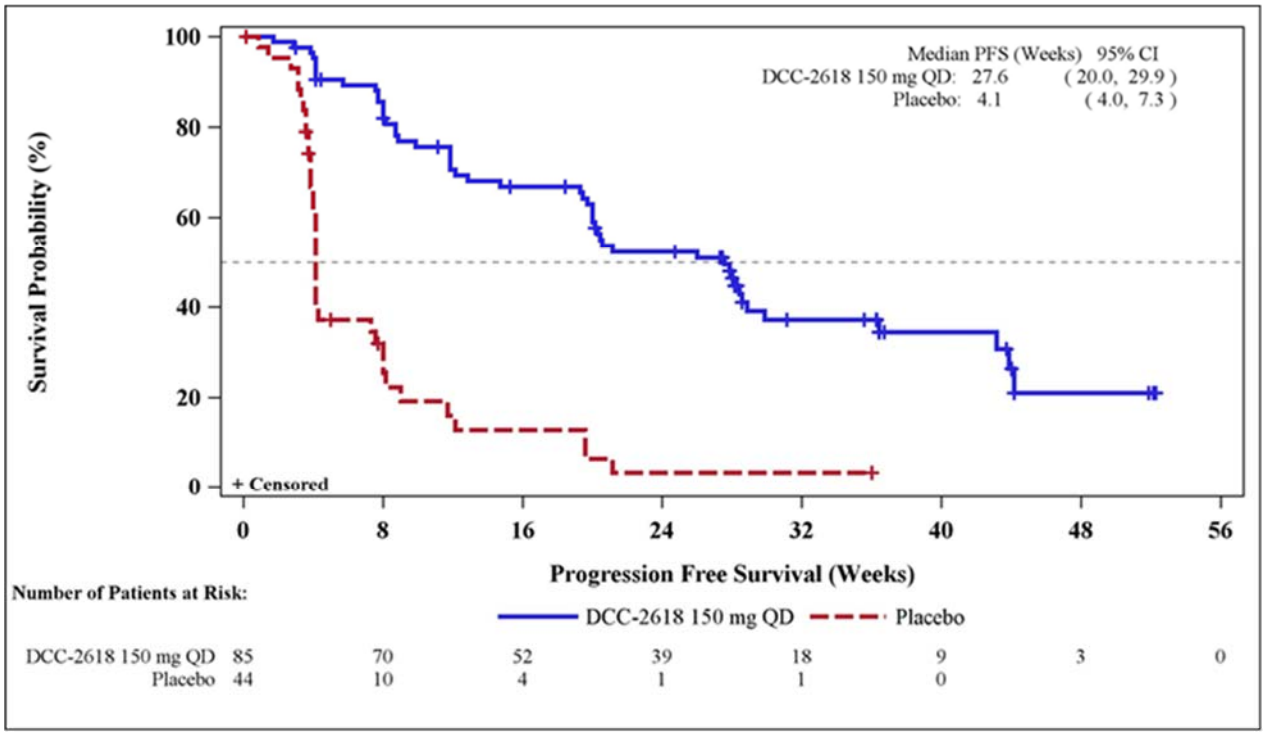
Table 9: Study DCC-2618-03-001: Progression-Free Survival Based on IRR in Double-blind Period (ITT Population)

Categories	Statistics	Placebo (N=44)	Ripretinib (N=85)	Ripretinib vs Placebo
Number of Patients with Event	n (%)	37 (84.1)	51 (60.0)	--
Number of Patients Censored	n (%)	7 (15.9)	34 (40.0)	--
Kaplan-Meier Estimate of Progression-Free Survival (Weeks)	25th Percentile (95% CI)	3.7 (3.1, 4.0)	11.9 (8.0, 19.3)	--
	Median (95% CI)	4.1 (4.0, 7.3)	27.6 (20.0, 29.9)	--
	75th Percentile (95% CI)	8.1 (4.1, 19.6)	44.1 (36.4, NE)	--
Log-Rank Test	p-value [1]	--	--	<0.0001
Cox Proportional Regression Model [2]	Hazard Ratio	--	--	0.15
	95% CI [3]	--	--	0.09, 0.25
Progression-Free Survival Rate				
26 Weeks	% (95% CI)	3.2 (0.2, 13.8)	51.0 (39.4, 61.4)	--
39 Weeks	% (95% CI)	NE (NE, NE)	34.4 (22.9, 46.2)	--
52 Weeks	% (95% CI)	NE (NE, NE)	21.0 (9.0, 36.3)	--

Abbreviations: CI = confidence interval; IRR = independent radiological review; ITT = intention-to-treat; NE = not estimable.

[1] p-value is based on 2-sided stratified log -rank test.
[2] Cox regression model includes treatment and randomization stratification factors as fixed factors.
[3] 95% CI is based on Wald Method.
Note 1: Progression-free survival is defined as the time interval between the date of randomization and the earliest documented evidence of the first disease progression based on the independent radiologic review or death due to any cause on initially assigned study treatment, whichever comes earlier. Progression-free survival may be censored as specified in the statistical analysis plan.
Note 2: Patient groups are based on the treatment initially assigned.
Source: DCC-2618-03-001 CSR, Table 21

Figure 3: Study DCC-2618-03-001: Kaplan-Meier Plot of Progression-Free Survival Based on IRR in Double-blind Period (ITT Population)



Abbreviations: CI = confidence interval; DCC-2618 = ripretinib; IRR= independent radiological review; ITT = intention-to-treat; PFS = progression-free survival; QD = once daily.
Data cutoff date: 31 May 2019.
Source: DCC-2618-03-001 CSR, Figure 14.2.1.1; Listing 16.2.6.5.1

The Applicant's Position:

Sensitivity Analyses:

Similar results were seen for PFS based on investigator assessment in the ITT population during the double-blind period. Median (95% CI) PFS per investigator assessment was 20.4 (18.4, 35.6) weeks in the ripretinib arm and 4.1 (3.9, 6.0) weeks in the placebo arm (hazard ratio = 0.19; $p < 0.0001$).

APPEARS THIS WAY ON ORIGINAL

Discordance between the IRR and the investigator assessment for progressive disease in double-blind period is provided in Table 10. Discordance was 20.2% overall in the double-blind period. In 17 (13.2%) patients, the investigator-assessed response was No Progressive Disease when the IRR-assessed response was Progressive Disease; in 9 (7.0%) patients, the IRR-assessed response was No Progressive Disease when the investigator-assessed response was Progressive Disease.

Table 10: Study DCC-2618-03-001: Discordance between IRR and Investigator Assessment for Progressive Disease in Double-blind Period (ITT Population)

Investigator Assessment	Independent Radiologic Review		Total N = 129
	Progressive disease n(%)	No progressive disease n(%)	
Progressive disease	64 (49.6)	9 (7.0)	73 (56.6)
No progressive disease	17 (13.2)	39 (30.2)	56 (43.4)

Abbreviations: IRR= independent radiological review; ITT = intention-to-treat.
Note: The percentages are based on the total number of patients in the ITT population.
Source: DCC-2618-03-001 CSR, Table 14.2.1.6

The Regulatory Authorities' Assessment:

The primary endpoint for study DCC-2618-03-001 was PFS based on disease assessment by blinded independent central review using modified RECIST v1.1 (previously defined).

FDA's primary efficacy analysis was based on 129 patients who received ripretinib 150 mg qd (n=85) or placebo (n=44).

With a HR of 0.15, the median PFS of 27.6 weeks (6.3 months) in the ripretinib arm versus 4.1 weeks (1 month) in the placebo arm demonstrates a statistically significant and clinically meaningful improvement in PFS for the indicated patient population [p-value <0.0001; p-value based on log-rank test stratified by prior lines of therapy (3 versus ≥4) and ECOG performance status (0 versus 1 or 2).

Data Quality and Integrity

The Applicant's Position:

No data integrity concerns were reported.

The Regulatory Authorities' Assessment:

The Regulatory Authorities agree with the Applicant's assessment.

Efficacy Results – Secondary and other relevant endpoints

The Applicant's Position:

Table 11 summarizes the results of the analyses of the secondary endpoints seen with ripretinib in Study DCC-2618-03-001. Ripretinib demonstrated an ORR of 9.4% compared with 0% for placebo (p-value = 0.0504), which was not statistically significant. However, ripretinib in this study also showed a clinically meaningful improvement over placebo in terms of the secondary endpoint OS (median OS 65.6 weeks vs. 28.6 weeks, HR = 0.36, nominal p-value = 0.0004). Because of the prespecified hierarchical alpha spending plan for secondary endpoints and since statistical significance was not achieved for ORR, the hypothesis testing of OS was not formally performed.

Table 11: Study DCC-2618-03-001: Results of Secondary Endpoints

	Study DCC-2618-03-001 Double-blind Period	
	Ripretinib (N=85)	**Placebo (N=44)**
Objective Response Rate (based on IRR)		
Complete Response, n (%)	0	0
Partial Response, n (%)	8 (9.4)	0
Objective Response Rate, n (%)	8 (9.4)	0
95% CI[c]	4.2, 17.7	0.0, 8.0
Fisher's Exact Test p-value[d]	Ripretinib vs Placebo: 0.0504	
Difference in Objective Response Rate, %	9.4	
95% CI[e]	0.2, 17.5	
Duration of Response		
Number of Patients with Event	1 (1.2)	0
Number of Patients Censored	7 (8.2)	0
Median Kaplan-Meier Estimate of Overall Survival (weeks)	NE	NE
95% CI	16.0, NE	NE, NE
Overall Survival		
Number of Patients with Event	26 (30.6)	26 (59.1)
Number of Patients Censored	59 (69.4)	18 (40.9)
Median Kaplan-Meier Estimate of Overall Survival (weeks)	65.6	28.6
95% CI	53.6, 65.6	17.9, 50.4
Log-rank test p-value[a]	Ripretinib vs Placebo 0.0004	

	Study DCC-2618-03-001 Double-blind Period	
	Ripretinib (N=85)	**Placebo (N=44)**
Hazard Ratio (95% CI)[b]	Ripretinib vs Placebo 0.36 (21, 0.62)	
Quality of Life: EORTC-QLQ-30		
Role Functioning Score-mean change from baseline to C2D1 (SD)	3.3 (27.31)	-17.2 (30.38)
Physical Functioning Score-mean change from baseline to C2D1 (SD)	1.5 (16.03)	-9.0 (19.28)

Abbreviations: CI = confidence interval; HR = hazard ratio; IRR = independent radiological review; ITT = intention-to-treat; NE=not estimable.
[a]p-value is based on 2-sided stratified log -rank test.
[b]Cox regression model includes treatment and randomization stratification factors as fixed factors. 95% CI is based on Wald Method.
[c]95% CI is exact binomial confidence interval.
[d]p-value is based on Fisher's exact test.
[e]95% CI is Newcombe Score confidence interval of the difference in objective response rate between the treatment arms.
Note 1: Progression-free survival is defined as the time interval between the date of randomization and the earliest documented evidence of the first disease progression based on the independent radiologic review or death due to any cause on initially assigned study treatment, whichever comes earlier. Progression-free survival may be censored as specified in the statistical analysis plan.
Note 2: Objective Response Rate is defined as the proportion of patients with a confirmed complete response or partial response based on the independent radiologic review and during the initial assigned study treatment.
Note 3: Overall Survival is defined as the time interval between the date of randomization until the date of death or censored at the date of last follow-up.
Patients groups are based on the treatment initially assigned.
Note 4: Duration of response is defined as the time from the first complete response or partial response which was subsequently confirmed until the time of disease progression or death by any cause. Duration of response may be censored as specified in the statistical analysis plan.
Note 5: Patient groups are based on the treatment initially assigned.
Source: DCC-2618-03-001 CSR, Table 14.2.2.1.1, Table 14.2.4, Table 14.2.8.1, Table 14.2.11

The data from Study DCC-2618-03-001 show that ripretinib provides a meaningful benefit to patients with advanced GIST. These data show a robust improvement in PFS and, although not subject to formal statistical testing, a clinically meaningful improvement in OS in a fourth-line disease setting where no other therapeutic options currently exist.

The efficacy profile presented in this NDA provides substantial evidence to support full approval of ripretinib for the proposed indication of treatment of patients with advanced GIST who have received prior treatment with imatinib, sunitinib, and regorafenib.

The Regulatory Authorities' Assessment:

The key secondary endpoints of Study DCC-2618-03-001 were overall response rate (ORR) assessed by independent radiologic review and overall survival (OS). The ORR for the ripretinib arm was 9.4% but was not significant compared to the alpha boundary of 0.047 (p-value 0.0504). DOR was not reached in either arm of the study. Although the results for OS shows an 8 month difference in median OS, a statistical difference in OS cannot be claimed due to no alpha allocated for the OS testing according to the prespecified hierarchal testing order.

Dose/Dose Response

The Applicant's Position:

Not applicable.

The Regulatory Authorities' Assessment:

This section is not applicable.

Durability of Response/Persistence of Effect

The Applicant's Position:

Long-term studies with ripretinib have not been conducted. Both Study DCC-2618-03-001 and Study DCC-2618-01-001 continue to evaluate ongoing patients as defined by the protocols.

The available data do not permit an analysis of the effect of drug over time after treatment is stopped or withheld.

The Regulatory Authorities' Assessment:

The Regulatory Authorities agree with the Applicant's assessment.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The Applicant's Position:

Analysis of Quality of Life assessments by the EORTC-QLQ-C30 and EQ-5D-5L were secondary endpoints and are presented in Table 11. Changes from baseline in disease related symptoms and quality of life scores tended to favor the ripretinib arm compared to the placebo arm.

The Regulatory Authorities' Assessment:

The Applicant did not include a PRO endpoint in their statistical hierarchical testing and did not prespecify any PRO analyses. While the results of the PRO analyses appear to be generally supportive of a favorable risk:benefit assessment, these analyses are considered descriptive.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:

Not applicable

The Regulatory Authorities' Assessment:

This section is not applicable.

8.1.3. DCC-2618-01-001 (Supportive Phase 1 Study in Patients with Advanced Malignancies)

Trial Design

Study DCC-2618-01-001 is an open-label Phase 1 study. The study started with an Escalation Phase evaluating increasing doses of single-agent ripretinib administered in repeated 28-day cycles in patients with advanced malignancies with a molecular rationale for activity. The Escalation Phase was followed by an Expansion Phase testing for further safety, PK, pharmacodynamic, and evidence of antitumor activity across a variety of tumors with evidence of alterations in genes that are targets of ripretinib.

The dose escalation phase started with an oral 20 mg BID dose of ripretinib. Safety data collected during the Escalation Phase were reviewed and monitored by a Safety Review Team (SRT). Three dose-limiting toxicities (DLTs) of asymptomatic Grade 3 lipase increased (n = 2) and asymptomatic Grade 4 creatine phosphokinase (CPK) increased (n = 1) were reported. No MTD was reached as there were < 33% of DLTs at each dose level explored. Based on in vivo and in vitro pharmacology studies in an interim population PK analysis, 150 mg QD was predicted to maintain the PK exposure above the presumed threshold for efficacy in > 90% of patients.

Patients assigned to a dose level may have escalated to a higher dose level that had subsequently been found to be safe and tolerable.

In the Expansion Phase, additional patients were enrolled in disease specific cohorts for KIT or PDGFRA mutant GIST, systemic mastocytosis (SM) and other hematologic malignancies, malignant gliomas, and other solid tumors. Patients started ripretinib at the RP2D (150 mg QD) in the Expansion Phase to further evaluate the safety, tolerability, and preliminary evidence of antitumor response. PET scans were performed for GIST patients that progressed and dose escalated. Dose escalation to 150 mg BID was allowed upon disease progression.

8.1.4. Study Results: Supportive Phase 1 Study DCC-2618-01-001

Data analyses in patients with advanced GIST from the interim clinical study report with a data cut-off of 01 March 2019, include a total of 142 patients with GIST who received 150 mg QD, of whom a total of 83 patients received ripretinib as a ≥ 4th line therapy.

Patients with advanced GIST (N = 142) who were treated at the RP2D of 150 mg QD had an ORR of 11.3% based on RECIST 1.1 by investigator assessment. The ORR for patients with GIST who received 150 mg QD was further examined by lines of therapy. The ORR was 7.2% in the 83 patients who received ripretinib as the ≥ 4th line therapy based on RECIST 1.1 by investigator assessment. The ORR was 19.4% in 2nd line patients (N = 31) and 14.3% in 3rd line patients (N = 28). The mean (standard deviation [SD]) time to response among all the responders was 19.2 (14.38) weeks.

The Kaplan-Meier estimate of median duration of response was 76.1 weeks among the 6 responders who received 150 mg QD as the ≥ 4th line of therapy in the Escalation and Expansion Phases; 4 patients remained in response as of the data cutoff date. The probability of maintaining response status for 52 weeks was 85.7% with 95% CI of 53.9%, 96.2%. The median duration of response for 2nd line patients was 80 weeks and was not estimable for 3rd line patients.

The Kaplan-Meier estimate of median (50th percentile) PFS was 23.9 weeks (95% CI = 15.9, 24.3) in patients with GIST who received 150 mg QD as the ≥ 4th line of therapy in the Escalation and Expansion Phases based on RECIST 1.1 by investigator assessment. The probability of maintaining PFS at 52 weeks was 21.7% with 95% CI of 13.1%, 31.6%. The median (50th percentile) PFS was 41.7 weeks for 2nd line patients and 36.3 weeks for 3rd line patients.

8.1.5. Integrated Review of Effectiveness

The Regulatory Authorities' Assessment:

The results of Study DCC-2618-01-001 are submitted as supportive data for this NDA. The ORR for patients who were randomized to receive ripretinib 150 mg QD in the 4th line setting was 7.2% and appears similar to the ORR of 9.4% observed in Study DCC-2618-03-001; however, the reviewers caution that cross-study comparisons are limited. The results of PFS for Study DCC-2618-01-001 are uninterpretable in this single-arm study due to the lack of a comparator arm and are considered descriptive only.

8.1.6. Assessment of Efficacy Across Trials

Data from DCC-2618-03-001 (pivotal study) and DCC-2618-01-001 (supportive study) are considered for evaluation of efficacy across clinical trials of ripretinib. Results presented here are from the double-blind period of Study DCC-2618-03-001. Because Study DCC-2618-01-001 included a dose escalation phase and enrolled patients with a variety of malignancies, the efficacy results from this study presented here include only results for patients with GIST who received ripretinib 150 mg QD in the ≥ 4th line setting. Together, these studies provide robust data to evaluate the efficacy of ripretinib at the recommended dose and in the target GIST patient population.

Efficacy endpoints across the 2 clinical studies are indicated in Table 12, with rationale for data presentation.

Table 12: Efficacy Criteria for Study DCC-2618-03-001 (Double-blind Period) and Study DCC-2618-01-001

Endpoint	Display	Rationale
Progression-Free Survival	Side-by-side	In Study DCC-2618-03-001: PFS based on IRR was the primary endpoint. A sensitivity analysis of PFS by Investigator assessment was performed. In Study DCC-2618-01-001: Analysis of PFS was based on Investigator assessment.
Objective Response Rate		In Study DCC-2618-03-001: ORR based on IRR was the key secondary endpoint. A sensitivity analysis of ORR by Investigator assessment was performed. In Study DCC-2618-01-001: Analysis of ORR was based on Investigator assessment.

Endpoint	Display	Rationale
Duration of Response		In Study DCC-2618-03-001: Analyses of DOR were performed based on both IRR and investigator assessment. In Study DCC-2618-01-001: Analysis of DOR was based on Investigator assessment.
Overall Survival	DCC-2618-03-001 only	This endpoint was only included in Study DCC-2618-03-001.
Time to Response	Separate analyses	In Study DCC-2618-03-001: Analysis of TTR was based on IRR. In Study DCC-2618-01-001: Analysis of TTR was based on Investigator assessment.
Time to Progression	DCC-2618-03-001 only	This endpoint was only included in Study DCC-2618-03-001.
Quality of Life Assessments		This endpoint was only included in Study DCC-2618-03-001.

Source: NDA Module 2.7.3, Table 1

A side-by-side comparison of PFS for Studies DCC-2618-03-001 and DCC-2618-01-001 is presented in Table 13.

In Study DCC-2618-03-001, the PFS was assessed by the IRR for the primary efficacy analysis, with median (95% CI) PFS as 27.6 (20.0, 29.9) weeks for the ripretinib arm and 4.1 (4.0, 7.3) weeks for the placebo arm (HR = 0.15; stratified log-rank test $p < 0.0001$). The median (95% CI) time for PFS by investigator assessment was 20.4 (18.4, 35.6) weeks for the ripretinib arm and 4.1 (3.9, 6.0) weeks for the placebo arm (HR = 0.19 with 95% CI [0.12, 0.32]). The comparison of PFS by investigator assessment between the treatment arms was consistent and supportive of the comparison of PFS by IRR.

In Study DCC-2618-01-001, the median (95% CI) progression-free survival (mPFS) by investigator assessment was 23.9 (15.9, 24.3) weeks in ≥ 4th line patients with GIST who received 150 mg QD ripretinib.

Overall, ripretinib improved median PFS based on IRR by 23.5 weeks compared to placebo in Study DCC-2618-03-001. The median PFS by Investigator assessment seen in Study DCC-2618-03-001 and Study DCC-2618-01-001 were supportive of the results seen by IRR in Study DCC-2618-03-001.

Table 13: Side-by-Side Comparison of Progression-Free Survival for Studies DCC-2618-03-001 and DCC-2618-01-001

	Pivotal Study Phase 3: DCC-2618-03-001 (Double-blind)				Supportive Study Phase 1: DCC-2618-01-001 (Open-label) 150 mg QD GIST patients ≥ 4th Line
	PFS by IRR		PFS by Investigator Assessment		PFS by Investigator Assessment
	Placebo N = 44	Ripretinib N = 85	Placebo N = 44	Ripretinib N = 85	Ripretinib N = 83
Number (%) of patients with event	37 (84.1)	51 (60.0)	36 (81.8)	45 (52.9)	64 (77.1)
Number (%) of patients censored	7 (15.9)	34 (40.0)	8 (18.2)	40 (47.1)	19 (22.9)
Median Kaplan-Meier estimate of PFS in weeks (95% CI)	4.1 (4.0, 7.3)	27.6 (20.0, 29.9)	4.1 (3.9, 6.0)	20.4 (18.4, 35.6)	23.9 (15.9, 24.3)
Log-Rank Test P-value [1]	< 0.0001		-		
Cox Proportional Regression Model [2] Hazard Ratio (95% CI [3])	0.15 (0.09, 0.25)		0.19 (0.12, 0.32)		

Abbreviations: CI = Confidence interval; GIST = gastrointestinal stromal tumor; IRR = Independent Radiologic Review; PFS = progression-free survival; QD = once daily.

[1] P-value is based on 2-sided stratified Log Rank test.

[2] Cox regression model includes treatment and randomization stratification factors as fixed factors.

[3] 95% CI is based on Wald Method.

Note 1: In Study DCC-2618-03-001, PFS was defined as the time interval between the date of randomization and the earliest documented evidence of the first disease progression or death due to any cause on initially assigned study treatment, whichever comes earlier. PFS may have been censored as specified in the statistical analysis plan. In Study DCC-2618-01-001 PFS was defined as the time in weeks from Cycle 1 Day 1 until disease progression (either disease progression per investigator radiologic assessment or clinical progression) or death from any cause.

Note 2: In Study DCC-2618-03-001, patient groups were based on the treatment initially assigned.

Note 3: In Study DCC-2618-01-001, line of therapy was determined by the number of individual treatment regimens received by the patient previously. If a patient received the same regimen more than once, even at a different dose, it was counted as a single line of treatment. If the same drug was combined with a second drug, it was counted as a separate line of therapy. A patient having received, for example, 3 distinct treatment regimens (single agent or combination) was considered a 4th line patient.

Source: NDA Module 2.7.3, Table 3

The Regulatory Authorities' Assessment:

The Regulatory Authorities consider the comparative analysis of PFS results presented above to be descriptive in nature. As previously stated in this review, results of PFS are uninterpretable in a single-arm study, and thus the results of Study DCC-2618-01-001 are not considered by FDA to demonstrate the clinical benefit of ripretinib.

FDA also considered the Applicant's proposed indication statement (b) (4) (b) (4). The Applicant referenced the results of the DCC-2618-01-001 trial as justification; this study included 3rd line patients. Ultimately, the FDA review team did not agree that the results of Study DCC-2618-01-001 were sufficient to support an assessment of benefit (b) (4) for similar reasons that preclude conclusive statements regarding whether this trial provided evidence in support of the benefit of ripretinib at the proposed dosage.

Secondary and Other Endpoints

A side-by-side comparison of ORR for Studies DCC-2618-03-001 and DCC-2618-01-001 is presented in Table 14. Note that Study DCC-2618-003-001 used mRECIST criteria and Study DCC-2618-01-001 used RECIST criteria for tumor assessment.

In Study DCC-2618-03-001, based on IRR, a total of 8 (9.4%) patients in the ripretinib arm and 0 patients in the placebo arm had an objective response; the difference in ORR by IRR was not statistically significant (p-value = 0.0504, Fisher's exact test). Based on the Investigator assessment, a total of 9 (10.6%) patients in the ripretinib arm and 0 patients in the placebo arm had an objective response.

In Study DCC-2618-01-001, a total of 6 (7.2%) ≥ 4th line patients with GIST treated with 150 mg QD ripretinib had a confirmed partial response as assessed by Investigator assessment.

In summary, ripretinib demonstrated an ORR by IRR of 9.4% compared with 0% for placebo (p-value = 0.0504, Fisher's exact test); however, this failed to reach statistical significance. The ORR by Investigator assessment was consistent with the ORR by IRR in Study DCC-2618-03-001 and ORR by Investigator assessment in Study DCC-2618-01-001.

Table 14: Side-by-Side Comparison of Objective Response Rate for Studies DCC-2618-03-001 and DCC-2618-01-001

	Pivotal Study Phase 3: DCC-2618-03-001 (Double-blind)				Supportive Study Phase 1: DCC-2618-01-001 (Open-label) 150 mg QD GIST Patients ≥ 4th Line
	ORR by IRR		ORR by Investigator Assessment		ORR by Investigator Assessment
Categories	Placebo (N = 44)	Ripretinib (N = 85)	Placebo (N = 44)	Ripretinib (N = 85)	(N = 83)
Complete Response – n (%)	0	0	0	0	0
Confirmed Partial Response – n (%)	0	8 (9.4)	0	9 (10.6)	6 (7.2)
Stable Disease (≥ 6 Weeks) – n (%)	9 (20.5)	56 (65.9)	8 (18.2)	48 (56.5)	49 (59.0)
Progressive Disease – n (%)	28 (63.6)	16 (18.8)	28 (63.6)	21 (24.7)	22 (26.5)
Not Evaluable – n (%)	3 (6.8)	4 (4.7)	4 (9.1)	6 (7.1)	1 (1.2)
No Response Assessment – n (%)	4 (9.1)	1 (1.2)	4 (9.1)	1 (1.2)	5 (6.0)
Objective Response Rate	0	8 (9.4)	0	9 (10.6)	6 (7.2)
95% CI [1]	(0.0, 8.0)	(4.2, 17.7)	(0.0, 8.0)	(5.0, 19.2)	(2.7, 15.1)
Fisher's Exact Test p-value [2]	0.0504		-		
Difference in Objective Response Rate % (95 % CI) [3]	9.4 (0.2, 17.5)		10.6 (1.2, 18.9)		

Abbreviations: CI = confidence interval; GIST = gastrointestinal stromal tumor; ORR = objective response rate; QD = once daily.

[1] 95% CI is an exact binomial CI.

[2] P-value is based on Fisher's exact test.

[3] 95% CI is Newcombe Score confidence interval of the difference in objective response rate between the treatment arms.

Note 1: In Study DCC-2618-03-001, ORR was defined as the proportion of patients with a confirmed complete response or PR and during the initial assigned study treatment. In Study DCC-2618-01-001, ORR was defined as proportion of patients who have a confirmed complete or partial response.

Note 2: In Study DCC-2618-03-001, patient groups were based on the treatment initially assigned.

Note 3: In Study DCC-2618-01-001, line of therapy was determined by the number of individual treatment regimens received by the patient previously. If a patient received the same regimen more than once, even at a different dose, it was counted as a single line of treatment. If the same drug was combined with a second drug, it was counted as a separate line of therapy. A patient having received, for example, 3 distinct treatment regimens (single agent or combination) was considered a 4th line patient.

Source: NDA Module 2.7.3, Table 4

A side-by-side comparison of DOR for Studies DCC-2618-03-001 and DCC-2618-01-001 is presented in Table 15.

In Study DCC-2618-03-001, the median DOR in the ripretinib arm was not yet reached at the data cut-off. Per IRR, of the 8 responders in the ripretinib arm, 6 were still in response, 1 progressed, and 1 patient who had a partial response was censored (patient underwent surgical management). There were no responders in the placebo arm. Similar results were seen for DOR by Investigator assessment in this study.

In Study DCC-2618-01-001, the KM estimate of median (95% CI) DOR was 76.1 (24.1, NE) weeks in patients with GIST who received 150 mg QD as the ≥ 4th line of therapy in the Escalation and Expansion Phases; 4 patients were still in response as of the data cut-off.

Table 15: Side-by-Side Comparison of Duration of Response for Studies DCC-2618-03-001 and DCC-2618-01-001

	Pivotal Study **Phase 3: DCC-2618-03-001** **(Double-blind)**				**Supportive Study** **Phase 1: DCC-2618-01-001** **(Open-label)** **150 mg QD** **GIST patients ≥ 4th Line**
	DOR by IRR		**DOR by Investigator Assessment**		**DOR by Investigator Assessment**
	Placebo N = 44	**Ripretinib N = 85**	**Placebo N = 44**	**Ripretinib N = 85**	**Ripretinib N = 83**
Number (%) of patients with event	0	1 (1.2)	0	2 (2.4)	2 (2.4)
Number (%) of patients censored	0	7 (8.2)	0	7 (8.2)	4 (4.8)
Median Kaplan-Meier estimate of PFS in weeks (95% CI)	NE (NE, NE)	NE (16.0, NE)	NE (NE, NE)	NE (11.9, NE)	76.1 (24.1, NE)

Abbreviations: CI = Confidence interval; DOR = duration of response; GIST = gastrointestinal stromal tumor; NE = not estimable; QD = once daily.

Note 1: Duration of response was defined as the time from the first complete response or partial response which was subsequently confirmed until the time of disease progression or death by any cause. For Study DCC-2618-03-001, duration of response may have been censored as specified in the statistical analysis plan.

Note 2: In Study DCC-2618-03-001, patient groups were based on the treatment initially assigned.

Note 3: In Study DCC-2618-01-001, line of therapy was determined by the number of individual treatment regimens received by the patient previously. If a patient received the same regimen more than once, even at a different dose, it was counted as a single line of treatment. If the same drug was combined with a second drug, it

was counted as a separate line of therapy. A patient having received, for example, 3 distinct treatment regimens (single agent or combination) was considered a 4th line patient.
Source: NDA Module 2.7.3, Table 5

The Regulatory Authorities' Assessment:

The Regulatory Authorities do not object to the Applicant's presentation of the results of the ORR analyses in studies DCC-2618-01-001 and DCC-2618-03-00. However, as previously stated in this review, FDA cautions against cross-study comparisons in the results due to the limitations inherent in such comparisons due to differences between the studies. For example, there are differences in patient populations: patients were required to have received any 3 prior therapies in Study DCC-2618-01-001 while patients in Study DCC-2618-03-001 must have received all three FDA-approved therapies in. The disease response criteria also differed across the studies (i.e., modified RECIST v1.1 versus RECIST v1.1).

Subpopulations

In Study DCC-2618-03-001, the following subgroup analyses were performed for PFS and ORR:

Age (18 – 64 vs 65 – 74 vs 75 years or older)

Gender (male vs female)

Race (White vs non-White vs not reported)

Region (US vs non-US)

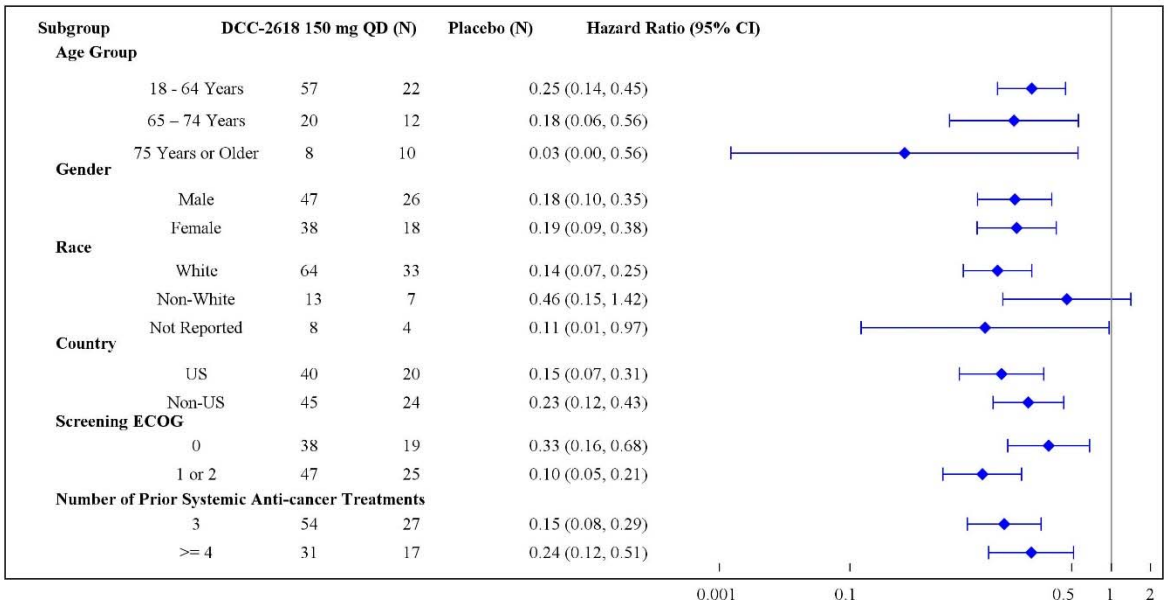
Screening ECOG (0 vs 1 or 2)

Number of prior therapies (3 vs ≥ 4)

The ripretinib arm showed benefit in all assessed patient subgroups for PFS (hazard ratio < 1) and ORR (difference > 0) in Study DCC-2618-03-001 (Figure 4, Figure 5).

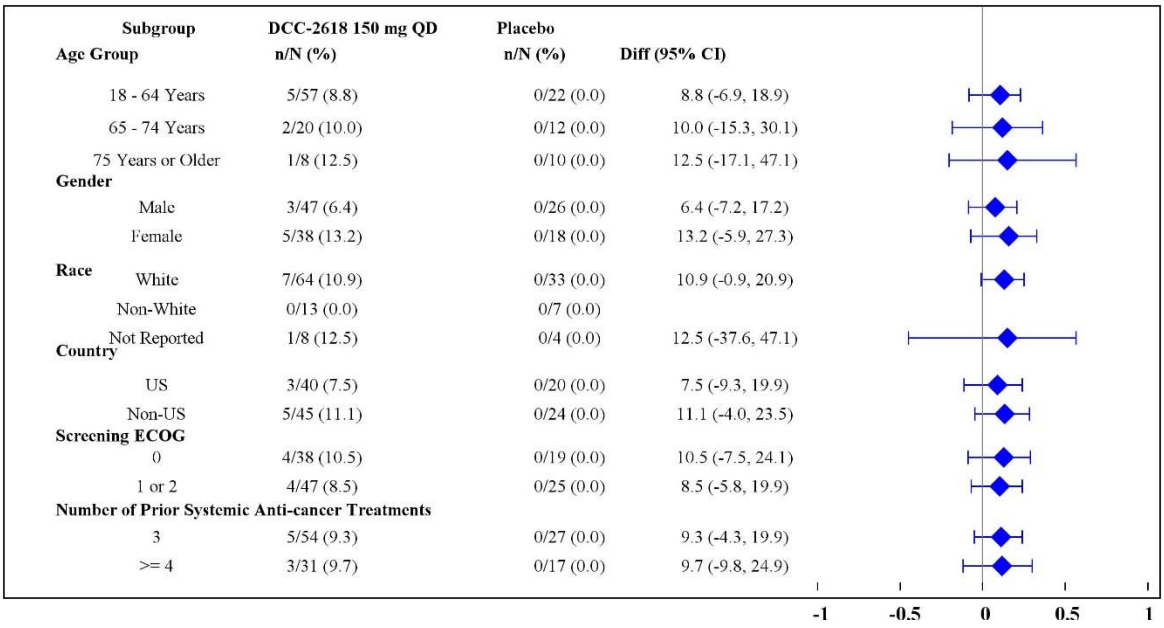
Subgroup analyses were not performed in Study DCC-2618-01-001.

Figure 4: DCC-2618-03-001: Forest Plot of Progression-free Survival Based on Independent Radiologic Review in Double-blind Period in Patient Subgroups (ITT Population)



Abbreviations: CI = confidence interval; DCC-2618 = ripretinib; ECOG = Eastern Cooperative Oncology Group; ITT = intention-to-treat.
Data cutoff date: 31 May 2019.
Source: DCC-2618-03-001 CSR, Figure 4

Figure 5: DCC-2618-03-001: Forest Plot of Objective Response Rate Based on IRR in Patient Subgroups (ITT Population)



Abbreviations: DCC-2618 = ripretinib; IRR= independent radiological review; ITT = intention-to-treat.
Data cutoff: 31 May 2019.
Source: DCC-2618-03-001 CSR, Figure 6

The Regulatory Authorities' Assessment:

The Regulatory Authorities agree with the Applicant's subgroup analyses presented above. Given the differences in the proportion of older patients enrolled on the placebo arm, the review team performed additional analyses to assess any potential impact of age on PFS, ORR, and OS. The tables below present the results for pre-specified subgroups of age.

PFS, OS in pre-specified subgroups of age:

Age group	N (Ripretinib vs Placebo)	% Events		Median in months (95% CI)		HR (95% CI)
		Ripretinib	Placebo	Ripretinib	Placebo	
PFS						
18 - 64 years	79 (57 vs. 22)	59.7%	86.4%	6.3 (4.6, 10)	1.3 (1, 2.7)	0.25 (0.14, 0.45)
65 – 74 years	32 (20 vs. 12)	60%	75%	4.5 (1.8, NE)	1 (0.8, 1.8)	0.17 (0.06, 0.54)
≥75 years	18 (8 vs. 10)	62.5%	90%	6.5 (1.8, 8)	0.8 (0.6, 1)	-*
OS						

18 - 64 years	79 (57 vs. 22)	31.6%	63.6%	12.3 (10, NE)	5.7 (1.8, NE)	0.33 (0.16, 0.66)
65 – 74 years	32 (20 vs. 12)	30%	58.3%	15.1 (7, 15)	9.2 (4.1, 12)	0.4 (0.13, 1.28)
≥75 years	18 (8 vs. 10)	25%	50%	NE (5, NE)	4.8 (1, NE)	0.3 (0.06, 1.57)

*HR was not presented for this subgroup due to small sample size.

ORR in pre-specified subgroups of age:

Subgroup	**N (Ripretinib vs Placebo)**	**ORR (%) (95% CI)**	
		Ripretinib	**Placebo**
18 - 64 years	79 (57 vs. 22)	9 (2.9, 19)	0 (0, 15)
65 - 74 years	32 (20 vs. 12)	10 (1.2, 32)	0 (0, 27)
≥75 years	18 (8 vs. 10)	13 (0.3, 53)	0 (0, 31)

Based upon the results of the analyses of the PFS, OS, and ORR endpoints by age subgroup, there appears to be no clinically meaningful differences in outcomes, but in some cases, the sample size is too small to reach any definitive conclusions.

8.1.7. Integrated Assessment of Effectiveness

The Applicant's Position:

APPEARS THIS WAY ON ORIGINAL

GISTs represent the most common form of sarcoma, a relatively rare subset of cancers arising from mesenchymal cells in the body. Despite recent progress and the availability of an increasing number of targeted kinase inhibitors, disease relapse resulting from drug resistance develops in most patients. At present, there are no approved targeted therapies that effectively inhibit many secondary drug□resistant mutations in GIST. Thus, a high medical need remains for developing kinase inhibitors that maintain high potency against these mutant forms of KIT and PDGFRα.

Ripretinib demonstrated statistically significant and clinically meaningful improvement in PFS compared to placebo as determined by IRR. Median PFS was 27.6 weeks in the ripretinib arm compared to 4.1 weeks in the placebo arm and significantly reduced the risk of disease progression or death by 85% (HR of 0.15, $p < 0.0001$) compared to placebo. The other clinically significant endpoints ORR and OS were not statistically significant (as discussed below) but showed large improvement when compared to placebo and prior therapies. Ripretinib demonstrated an ORR as determined by IRR using mRECIST version 1.1, of 9.4% compared with 0% for placebo (p-value = 0.0504), which was not statistically significant. However, ripretinib in this study also showed a clinically meaningful improvement over placebo in terms of the secondary endpoint OS (median OS 65.6 weeks vs. 28.6 weeks, HR = 0.36, nominal p-value =

0.0004). Because of the prespecified hierarchical alpha spending plan for secondary endpoints and since statistical significance was not achieved for ORR, the hypothesis testing of OS was not formally performed. The efficacy data including PFS and ORR are consistent with what was observed in the patients with advanced GIST who received recommended dose of 150 mg QD of ripretinib as ≥ 4th line of therapy in the Phase 1 Study.

The data from the DCC-2618-03-001 study, supported by data from the Phase 1 study (Study DCC-2618-01-001) show that ripretinib provides a meaningful benefit to patients with advanced GIST in a fourth-line disease setting where no other therapeutic options currently exist. These data show a robust improvement in median PFS and, although not subject to formal statistical testing, the data demonstrate that ripretinib shows a clinically meaningful improvement in OS in the post-imatinib setting.

The efficacy profile presented here provides substantial evidence to support full approval of ripretinib for the proposed indication of treatment of patients with advanced GIST who have received prior treatment with imatinib, sunitinib, and regorafenib.

The FDA's Assessment:

The FDA agrees that ripretinib demonstrated a statistically significant and clinically meaningful improvement in PFS over placebo for patients with advanced GIST who received prior treatment with imatinib, sunitinib, and regorafenib as demonstrated in Study DCC-2618-03-001. FDA agrees that the results of Study DCC-2618-03-001 provide supportive evidence of the benefit of ripretinib in the indicated population. The analysis of efficacy by prior line of therapy appears to demonstrate activity across heavily pre-treated patients with GIST (i.e., 3 versus ≥ 4). Kinase inhibitors targeting KIT and PDGFR have been used successfully to treat patients with GIST, as evidenced by the previous approvals of imatinib, sunitinib, and regorafenib in the first, second, and third line setting, respectively. However, there are no approved therapies for patients who have exhausted these (i.e., the 4th line setting and beyond) and thus, ripretinib addresses an unmet medical need in this patient population.

8.2. Review of Safety

The Applicant's Position:

The safety evaluation is based on data from 446 subjects with any exposure to ripretinib across 4 clinical studies. The primary focus on data from the 128 patients treated during the double-blind period of the pivotal study, Study DCC-2618-03-001 (including 85 patients treated with 150 mg QD ripretinib and 43 patients treated with placebo). Additional safety analyses were performed on the integrated safety population, which includes patients who were enrolled in

the supportive Phase 1 study. The integrated population of patients with any exposure to ripretinib includes 351 patients, and the integrated population of patients with GIST exposed to 150 mg ripretinib includes 256 patients.

In addition, 95 subjects were exposed to at least 1 dose of ripretinib in the 2 healthy subject studies (DCC-2618-01-002 and DCC-2618-01-003). The safety data from these 2 studies did not reveal any additional findings that would affect the safety profile of ripretinib.

Data from these studies allow for an informed assessment of the safety profile of ripretinib and an evaluation of the overall benefit-risk in patients with advance GIST. This safety population is also considered appropriate for the detection and characterization of common AEs and to provide guidance on toxicity management.

The Regulatory Authorities' Assessment:

The Regulatory Authorities acknowledge and agree with the Applicant's description of the safety population.

8.2.1. Safety Review Approach

The Applicant's Position:

Adverse events of clinical importance (AECI) pooled from DCC-2618-03-001 and DCC-2618-01-001 include categories which were based on the class effect, mechanism of action, and the clinical experience to date with ripretinib. These categories were used to evaluate the risks of ripretinib. The risks of ripretinib include important identified risks associated with ripretinib treatment include, hand-foot skin reaction (HFSR) [PPES] and hypertension. An important potential risk associated with ripretinib treatment was squamous cell carcinoma (SCC) of skin. These events were managed by appropriate supportive medical care and/or dose modifications. Identified risks include alopecia, myalgia, arthralgia and diarrhea. Potential risks include cardiac failure, hyperbilirubinemia and Stevens-Johnson syndrome.

The Regulatory Authorities' Assessment:

The primary data used by FDA to assess and characterize the safety of ripretinib at the proposed recommended dose (150 mg once daily until disease progression, unacceptable toxicity, or death) is derived from the double blinded period of the pivotal trial, DCC-2618-03-001, in which 85 patients received at least 1 dose of ripretinib and 43 patients received at least one dose of placebo.

Key inclusion criteria for this study impacting interpretation of safety data include:

- Absolute neutrophil count ≥ 1000/uL
- Hemoglobin ≥ 8 g/dL
- Platelet count ≥ 75,000/uL
- Total bilirubin ≤ 1.5 x the upper limit of normal (ULN)
- Aspartate transaminase and alanine transaminase ≤ 3 x ULN (≤ 5x ULN in the presence of hepatic metastases
- Serum creatinine ≤ 1 x ULN or creatinine clearance ≥ 50 mL/min based on urine collection of Cockcroft Gault estimation
- Prothrombin time (PT), international normalized ratio (INR), and partial thromboplastin time ≤ 1.5 x ULN.

Key exclusion criteria impacting interpretation of safety data include:

- New York Heart Association class II-IV heart disease, active ischemia or any other uncontrolled cardiac condition such as angina pectoris, cardiac arrhythmia requiring therapy, uncontrolled hypertension, or congestive heart failure.
- Arterial thrombotic or embolic events such as cerebrovascular accident or hemoptysis within 6 months before the first dose of study drug.
- Venous thrombotic events within 3 months before the first dose of study drug.
- QTc > 450 ms in males or > 570 ms in females or history of long QT interval corrected syndrome.

The protocol included dose modifications for dermatologic toxicities, arthralgia/myalgia, hypertension, and Other. The protocol specified dose modifications for toxicity are summarized as follows:

- Dermatologic toxicities and arthralgia/myalgia
    - Grade 4, (and Grade 3 Stevens-Johnson Syndrome) permanently discontinue study drug.
    - Grade 2 and 3, interrupt study drug for at least 7 days and until toxicity resolves to Grade 1 or baseline. Resume study drug at the same or decreased level depending on severity.
- Hypertension
    - Grade 4, permanently discontinue study drug
    - Grade 2 and 3, interrupt study drug if symptomatic. Resume study drug until symptoms resolve and diastolic BP ≤90 mmHg and/or systolic BP ≤140 mmHg. Resume study drug at the same or decreased level depending on severity.
- Other
    - Grade 3 and 4, interrupt study drug until toxicity resolves to Grade 1 or baseline. Resume study drug at reduced dose.
    - Clinically significant Grade 3 or 4 laboratory adverse events. Interrupt study

drug. Resume study drug based on patient's best interest after discussion with the Sponsor.

The integrated safety datasets comprise data derived from Study DCC-2618-03-001 and from Study DCC-2618-01-001, an open-label, single arm dose escalation with cohort expansion trial of ripretinib in patients with advanced malignancies. To confirm the Applicant's identified safety signals in the DCC-2618-03-001 trial and to identify any additional, rare, but potentially serious safety signals, FDA analyzed the pool of 351 patients with a diagnosis of advanced solid tumor who received at least one dose of ripretinib (Applicant's Pool 3 and referred to in this review as ISS). This pool comprises 85 patients randomized to receive ripretinib on DCC-2618-03-001, 29 patients randomized to receive placebo in DCC-2618-03-001 and crossed over to received ripretinib after confirmed progression, and 237 patients enrolled in escalation cohorts or expansion cohorts of Study DCC-2618-01-001. Of these patients, 98% received a cumulative daily ripretinib dose of ≥ 100 mg. The analysis of adverse events for the 29 patients randomized to receive placebo who subsequently crossed over to receive ripretinib, was limited to adverse events occurring after the cross-over.

The FDA calculated the frequency of all adverse events at the PT, HLT, HLGT, and SOC MEDDRA levels as well as based on narrow, broad, and algorithmic SMQs.

The FDA considered objective data rather than adverse event reporting when evaluating toxicity for which objective data was available (e.g., laboratory values and vital signs).

8.2.2. Review of the Safety Database

Overall Exposure

The Applicant's Position:

The evaluation of safety of ripretinib is primarily based on the placebo-controlled data from the pivotal study, Study DCC-2618-03-001. To supplement the placebo-controlled data from Study DCC-2618-03-001, an integrated analysis of safety was performed incorporating safety data from Studies DCC-2618-03-001 and DCC-2618-01-001.

Double-Blind Period in Study DCC-2618-03-001

In the double-blind period of Study DCC-2618-03-001, a total of 128 patients received at least one dose of the assigned treatment per arm (ripretinib arm, N = 85; placebo arm, N = 43). One patient randomized to the placebo arm did not receive treatment, and therefore was not included in the safety population.

The mean (SD) treatment duration for the ripretinib arm (24.44 [13.941] weeks) was longer than the treatment duration for the placebo arm (8.25 [6.757] weeks), and the treatment duration ranged from 1.3 to 59.4 weeks and 0.4 to 38.4 weeks for the ripretinib and placebo arms respectively.

Table 16: Study DCC-2618-03-001: Treatment Exposure in Double-Blind Period (Safety Population)

Parameter	Statistics	Placebo (N = 43)	Ripretinib (N = 85)
Treatment Duration (weeks) [1]	N	43	85
	Mean (SD)	8.25 (6.757)	24.44 (13.941)
	Median	6.00	23.86
	Min, Max	0.4, 38.4	1.3, 59.4
Treatment Duration (months) [2]			
≥ 3 Months	n (%)	6 (14.0)	62 (72.9)
≥ 6 Months	n (%)	1 (2.3)	39 (45.9)
≥ 9 Months	n (%)	0	16 (18.8)
≥ 12 Months	n (%)	0	3 (3.5)
	Min, Max	84, 150	96, 150

Abbreviations: max = maximum; min= minimum; SD = standard deviation.

[1] Treatment duration (weeks) = (date of last treatment– date of first treatment + 1)/7. For patients who entered the open-label period, the end date of the double-blind treatment period is used as the date of last treatment for calculation.
[2] Treatment duration (months) = (date of last treatment – date of first treatment + 1)/30.4375. Date of last treatment is defined as in footnote [1].
Note: Patient groups are based on the treatment initially received.
Source: DCC-2618-03-001 CSR, Table 14.3.1.1

All Patients with Any Dose of Ripretinib in Studies DCC-2618-03-001 and DCC-2618-01-001 (Pool 3)

In Pool 3, the mean (standard deviation [SD]) duration of treatment for ripretinib administration for all patients was 33.4 (27.72) weeks (Table 17). Notably, 51.6% (181/351) of patients in Pool 3 received ripretinib treatment for ≥ 6 months in duration.

Table 17: Integrated Analysis Pool 3: Ripretinib Exposure by Analysis Pools (Safety Population)

		Pool 3
Characteristics	**Statistics**	**All Patients Any Dose (N=351)**
Treatment Duration (weeks) [a]	N	351
	Mean (SD)	33.4 (27.72)
	Median	28
	Min, Max	0, 171
Treatment Duration (months) [b]		
≥ 3 Months	n (%)	248 (70.7)
≥ 6 Months	n (%)	181 (51.6)
≥ 9 Months	n (%)	124 (35.3)
≥ 12 Months	n (%)	73 (20.8)
≥ 24 Months	n (%)	7 (2.0)
≥ 36 Months	n (%)	1 (0.3)

SD = standard deviation.
Note 1: Per the Phase 3 study protocol, dose escalation to 150 mg BID was not reported as a dose increase. However, in the Phase 1 protocol, dose escalation to 150 mg BID was reported as dose increase.
[a] Treatment duration (weeks) = (date of last treatment- date of first treatment + 1)/7. For patients who participated the food portion in Phase 1 study, the date of first treatment post the food portion is used for calculation and one day is added to the treatment duration.

[b] Treatment duration (months) = (date of last treatment- date of first treatment + 1)/30.4375. Date of first treatment is defined as in footnote [a].

Data cut-off date for study DCC-2618-01-001: 01MAR2019.

Data cut-off date for study DCC-2618-03-001: 31MAY2019.

The Regulatory Authorities' Assessment:

The FDA verified the Applicant's values reported in Table 16. Additional treatment exposure parameters are shown in the table below. The exposure to ripretinib was much longer than to placebo. FDA considers the exposure to ripretinib in terms of treatment duration, average daily dose, and dose intensity to be adequate to assess the safety of ripretinib in patients with GIST.

Additional Exposure Parameters in the Double-Blind Period of Study DCC-2618-03-001

Parameter	Ripretinib N=43	Placebo N-43
Number of cycles received (weeks)		
Mean (SD)	6.1 (3.5)	2.1 (1.7)
Median (min, max)	6.0 (0.3, 14.9)	1.5 (0.1, 9.6)
Average daily dose (mg)		
Mean (SD)	145 (11.4)	137 (17.90)
Median (min, max)	150 (96, 150)	146 (84, 150)
Dose Intensity (%)		
Mean (SD)	97 (7.6)	92 (12)
Median (min, max)	100 (64,100)	97 (56,100)

Source: Reviewer table based on DCC-2618-03-001: ADEX dataset

Relevant characteristics of the safety population:

The Applicant's Position:

The eligibility criteria in the pivotal Phase 3 Study DCC-2618-03-001 were clinically relevant for the target population of subjects who would receive ripretinib following regulatory approval in the proposed indication. The study enrolled patients with advanced GIST who have received prior anticancer treatment with imatinib, sunitinib, and regorafenib.

Demographic characteristics were well balanced between the two treatment groups (ripretinib versus placebo), thereby providing reassurance with regard to the interpretation of the treatment comparison and the validity of the safety conclusions.

Overall, the baseline characteristics were representative of the broad population of patients with advanced GIST.

The Regulatory Authorities' Assessment:

The Regulatory Authorities agree with the Applicant's assessment.

Adequacy of the safety database:

The Applicant's Position:

The evaluation of safety is based on data from the double-blind period of the Phase 3 pivotal study, Study DCC-2618-03-001 and supplemented with data from the supportive Phase 1 study, Study DCC-2618-01-001. Further details are provided in Section 8.2. This population allows for an informed assessment of the safety profile or ripretinib and a judgement of the overall benefit-risk in subjects with advanced GIST.

The Regulatory Authorities' Assessment:

The size of the safety database is adequate to provide a reasonable estimate of adverse reactions that may be observed with ripretinib 150 mg QD, and the duration of the treatment is adequate to allow assessment of adverse reactions over time. The safety database represents the gender, age, and race consistent with that observed in the overall population of patient who are diagnosed with GIST.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

No meaningful concerns are anticipated in the quality and integrity of the submitted datasets and individual case narratives; these were sufficiently complete to allow for a thorough review of safety. Furthermore, no data integrity concerns were reported following a completion of site inspections; data in the case report forms (CRFs) and AE databases were consistent.

The Regulatory Authorities Assessment:

FDA performed the following analyses to assess the quality and consistency of the safety data:

1) Comparison of coding: The FDA reviewer compared the coding of the actual reported term (AETERM) to the lowest level term in the MedDRA hierarchy (AELLT) for the 1390 treatment emergent adverse events that were reported during the double blinded

period in DCC-2618-03-001. With the exception of cutaneous squamous cell carcinoma, the coding was generally consistent and appropriate. Coding of likely cases of squamous cell carcinoma were inconsistently coded to "squamous cell carcinoma of head and neck" or "squamous cell carcinoma of skin". As a result, FDA identified 2 additional cases of cutaneous squamous cell carcinoma. FDA identified similar inconsistency in the ISS.

2) Comparison of Treatment Discontinuations due to adverse events as reported in the subject level ADSL, which includes patient disposition, and as reported in ADAE variable AECN (action taken) did not identify significant discrepancies.
3) Comparison of dose delays and modifications due to adverse events as reported in the exposure data file and as reported in adverse events did not identify significant discrepancies.
4) Comparison of assessment of relatedness to study treatment for fatalities and serious adverse events based on evaluation of narratives identified a limited number of cases where the reviewer did not agree with the Applicant's assessment. These differences did not impact the overall conclusion regarding fatal events but did impact the overall assessment of cardiac toxicity. This is discussed further in Section 8.2.5. .
5) FDA confirmed the safety results reported by the Applicant in this review and provided in the label, with the exception of frequency of cutaneous squamous cell carcinoma (see #1 above).

Categorization of Adverse Event

The Applicant's Position:

The safety of study treatment was evaluated on the basis of the:

- Frequency, type, severity, and causal relationship of AEs to study treatment
- AEs were graded using NCI CTCAE Version 4.03
- Frequency of deaths, SAEs, and other clinically significant AEs (including AEs leading to discontinuation and AEs requiring dose interruption and/or reduction)
- Frequency and type of AEs in key demographic subgroups (age, gender, race, geographic region, and BMI)
- Changes in laboratory variables, with particular attention to grade 3/4 abnormalities

Adverse events were classified according to the MedDRA Version 21.1.

Adverse events of clinical importance (AECIs) categories were selected based on the class effect, mechanism of action, and the clinical experience to date with ripretinib. These categories were used to evaluate the potential risks of ripretinib and are presented in Table 18.

For each AECI category, searches were performed using standardized MedDRA queries (SMQs), modified MedDRA SMQs, or custom MedDRA queries (CMQs) in order to retrieve relevant AEs.

Table 18: List of Adverse Events of Clinical Importance

Categories	Sub-Category
Cardiac Disorder	Cardiac failure
	Hypertension
Diarrhea	Diarrhea
Myalgia and Arthralgia	Arthralgia
	Myalgia
Dermatological Toxicities	Hand Foot Skin Reaction
	Alopecia
	Actinic Keratosis, Squamous cell carcinoma
	Stevens-Johnson syndrome
Lab Abnormalities	Hyperbilirubinemia

Source: NDA Module 2.7.4, Table 4

The clinical monitoring of subject safety was considered adequate for the expected toxicities associated with combination therapy with ripretinib. Patients were questioned about AEs at each clinic visit. In addition, AEs could also be detected when reported by the patients during or between visits or through laboratory test results and other assessments. Further to the standard safety evaluations outlined above, AECI categories were selected based on the class effect, mechanism of action, and the clinical experience to date with ripretinib. These categories were used to evaluate the potential risks of ripretinib.

<u>The Regulatory Authorities' Assessment:</u>

Per the Applicant's Summary of Clinical Safety (Table 4) included in the NDA, the Applicant used the following search strategies in identifying cases of the AECI:

- Cardiac Disorder

    - Cardiac Failure: Cardiac failure Broad and Narrow Scope SMQs
    - Hypertension: Hypertension Broad and Narrow Scope SMQs
- Diarrhea: Diarrhea (excl infective) HLT, Gastrointestinal infections HLGT
- Arthralgia: Joint related signs and symptoms HLT
- Myalgia: muscle pains HLT
- Dermatologic Toxicities
    - Hand Foot Syndrome: Epidermal and dermal conditions HLGT, Hyperkeratoses HLT
    - Alopecia: HLT Alopecias
    - Actinic Keratosis, Squamous cell carcinoma: Skin malignant tumors Broad and Narrow Scope SMQs, Skin premalignant disorders Broad and Narrow Scope SMQs
    - Stevens-Johnson syndrome Severe cutaneous adverse reactions Narrow Scope SMQ
- Hyperbilirubinemia: Biliary disorders Broad and Narrow scope SMQs.

Routine Clinical Tests

The Applicant's Position:

Hematology and chemistry laboratory assessment values were graded for severity according to NCI-CTCAE (v4.03) and summarized by shift in severity grade from baseline to the worst post-baseline. Laboratory measurements of alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphate (ALP), and total bilirubin were also evaluated for the potential risk of drug-induced liver injury. Potential Hy's Law cases were evaluated based on the following lab test results: ALT or AST > 3× upper limit of normal (ULN), total bilirubin ≥ 2× ULN, and ALP < 2× ULN.

The Regulatory Authorities' Assessment:

In the DCC-2618-03-001 trial, vital signs, weights, clinical laboratory tests including hematology, serum chemistries, and coagulation studies were to be evaluated Cycle 1 Days 1 (baseline) and 15) and Day 1 for subsequent cycles. 12-Lead ECG was to be performed Day 1 of each cycle. An echocardiogram or MUGA was to be performed at Cycle 3 Day 1 and every third cycle thereafter.

8.2.4. Safety Results

Deaths

The Applicant's Position:

A review of the deaths in Studies DCC-2618-03-001 and DCC-2618-01-001 did not identify any pattern as most subjects who died had underlying contributing comorbidities and complications associated with their disease. Most deaths were due to disease progression.

Study DCC-2618-03-001

Double-blind Period

In the double-blind period and long-term follow-up of Study DCC-2618-03-001, 25 patients died (12 patients in the ripretinib arm and 13 patients in the placebo arm). In both treatment arms, the majority of deaths were caused by disease progression (11 patients in each arm). Five (5.9%) patients in the ripretinib arm and 10 (23.3%) patients in the placebo arm had treatment emergent adverse events (TEAEs) leading to death during study treatment or within 30 days of the last dose.

Open-Label Period

Of the 29 patients who received placebo in the double-blind period and crossed over to receive ripretinib 150 mg QD in the open-label period, 5 (17.2%) patients died during the open-label period and 1 patient died during long-term treatment follow-up. All deaths were due to disease progression. Of the 11 patients who received ripretinib 150 mg QD in the double-blind period and continued to receive 150 mg QD in the open-label period, 4 (36.4%) patients died during the open-label period due to disease progression.

Of the 41 patients who dose escalated and received ripretinib 150 mg BID in the open-label period, 7 (17.1%) patients died during the open-label period and 9 patients died during long-term follow-up. Eight deaths were due to disease progression and 1 patient whose cause of death was unknown.

Study DCC-2618-01-001
At the time of the data cutoff, a total of 35 patients died in Study DCC-2618-01-001. In the Escalation Phase, 10 patients died including 8 patients with GIST, 1 patient with malignant glioma, and 1 patient with other solid tumors. Two deaths were due to metastatic gastrointestinal stromal tumor, 1 due to cardiac arrest, 2 due to progressive disease, 2 due to clinical progression, 2 unknown, and 1 lost to follow-up.

In the Expansion Phase, there were 25 deaths including 19 patients with GIST, 4 with malignant glioma, 1 with other solid tumor, and 1 with melanoma. Seven patients died due to disease progression, 2 patients died due to clinical progression, 2 patients died of progression of disease, and 2 due to unknown causes (not specified). The remaining 12 patient deaths (1 patient each) were due to unknown (per source), unknown (patient was discharged to hospice), sepsis, cholangitis, myocardial infarction, metastatic GIST, underlying disease, disease progression (patient passed away from their cancer), progression of GIST, clinical progressive disease, progression, and disease.

The Regulatory Authorities' Assessment:

Five fatal treatment emergent adverse events occurred in the ripretinib arm during the double blinded period of DCC-2618-01-001 (Death NOS (3), General Physical Health Decline (n=1), Hypoglycemia (n=1). Based on the narratives for these patients, FDA agrees that these deaths were due to progressive disease.

Sixteen fatal treatment emergent adverse events occurred in patients receiving ripretinib in the open-label period of DCC-2618-01-001. Nine occurred in patients receiving ripretinib 150 mg QD (Death (n=7), Internal hemorrhage (n=1), Respiratory failure (n=1). Seven fatal events occurred in patients receiving ripretinib 150 mg BID (Death (n=5), Gastric hemorrhage (n=1), multiple organ dysfunction syndrome (n=1)). Based upon review of the narratives and CFRs for these patients, FDA assessed that all 16 fatal adverse events were related to progression of GIST.

Twenty fatal TEAEs were reported in patients enrolled on Study DCC-2618-01-001 who received at least one dose of ripretinib. Review of the narratives for these patients indicates that 16 of the deaths were related to disease progression. For 1 death, the event of myocardial infarction is assessed by the Applicant and the reviewer as potentially related to ripretinib. For 3 deaths, the fatal events (cardiac arrest, cholangitis, and unknown) are assessed by the Applicant as unrelated to ripretinib; however, the reviewer finds insufficient information to rule out ripretinib as a contributing factor. The narratives for the 4 deaths not clearly due to disease progression are summarized below.

(b) (6)	The patient was a 60 year old female with a diagnosis of Stave IV metastatic GIST and medical history significant for ongoing tachycardia. The patient initiated treatment at 150 mg QD. On Study Day 286, the patient's dosage was increased to 150 mg BID. On day 455, the patient discontinued study drug due to progressive disease. On day 480, 27 days after receiving the last dose of study drug, the patient experienced a cardiac arrest outside of the hospital. Efforts to resuscitate the patient by emergency personnel were unsuccessful. Both the Investigator and the Applicant assessed the death due to cardiac arrest as unrelated to study treatment. This reviewer finds inadequate information to assess whether the fatal event of cardiac arrest is unrelated to ripretinib.
(b) (6)	The patient was a 70 year old male with diagnosis of GIST and medical history significant for ongoing hypertension, lipidemia, cardiac valve disease. On Study Day 29, the patient presented with hypotension and elevated

	creatinine and found to be septic. The patient was discharged from the hospital on Day 35 and ripretinib was resumed at the dosage of 150 mg QD. On day 41, the patient was admitted for severe hypotension. The patient was discharged the same day on hospice care. Study drug was not resumed. On day 51, 9 days after last dose of study drug, a family member reported the patient died. No further details were provided. The Investigator and the Applicant assessed the death as unrelated to study drug. This reviewer finds inadequate information to conclude that ripretinib did not contribute to the death; however, notes that the patient's entry to hospice care makes progressive disease a likely cause of death.
(b) (6)	The patient is a 56 year old male with diagnosis of GIST and medical history significant for ongoing hypercholesterolemia and diabetes mellitus. On Study Day 3, the patient complained of abdominal pain. On Day 4, the patient collapsed at home in cardiac arrest. Recitation was initiated by family member and continued by emergency personal but was ultimately unsuccessful. Final autopsy suggested cholangitis most likely due to an ascending infection leading to sepsis and subsequent cardiac arrest. The Investigator and Applicant assessed the fatal AE of cholangitis as not related to study drug; however, this reviewer does not find sufficient information to rule out ripretinib as a contributing factor. Of note, the adverse event of cardiac arrest was not reported as an adverse event.
(b) (6)	The patient is a 73 year old male with a diagnosis of Stage III spindle cell GIST with medical history significant for ongoing hypertension, chronic kidney disease, and 53-year smoking history. On day 169, echocardiogram showed LVEF of 62% with no wall abnormalities and normal right ventricular size and normal systolic function. On Study Day 195, an ECG showed NSR with evidence of left ventricular hypertrophy without ischemic changes. On Day 213, the patient experienced the SAE of myocardial infarction which ultimately resulted in the patient's death. The Investigator and Applicant assessed the adverse event of fatal myocardial infarction as possible related to the study drug. The reviewer concurs.

Source: DCC-2618-03-001: CSR and DCC-2618-01-001: CSR

Serious Adverse Events

The Applicant's Position:

Table 19 summarizes SAEs that occurred during the double-blind period of Study DCC-2618-03-001.

In the ripretinib arm, 26 (30.6%) patients experienced any SAE. The most commonly reported SAEs shown in ≥2 patients in the ripretinib arm were abdominal pain (4 [4.7%]), anemia (3 [3.5%]), death (3 [3.5%]), nausea (2 (2.4%]), and vomiting (2 (2.4%]).

In the placebo arm, 19 (44.2%) patients experienced any SAE. The most commonly reported SAEs shown in ≥2 patients in the placebo arm were death (4 [9.3%]), and abdominal pain, acute kidney injury, sepsis, and asthenia (2 [4.7%] patients each).

Note that if the cause of death was unknown, Death NOS was to be entered as the description for the AE.

Table 19: Study DCC-2618-03-001: Treatment-emergent Serious Adverse Events ≥ 2 Patients by Preferred Term in Double-blind Period (Safety Population)

Preferred Term	Placebo (N = 43) n (%)	Ripretinib (N = 85) n (%)
Any Treatment-emergent SAE	19 (44.2)	26 (30.6)
Abdominal pain	2 (4.7)	4 (4.7)
Anaemia	1 (2.3)	3 (3.5)
Death	4 (9.3)	3 (3.5)
Nausea	0	2 (2.4)
Vomiting	0	2 (2.4)
Acute kidney injury	2 (4.7)	1 (1.2)
Sepsis	2 (4.7)	1 (1.2)
Asthenia	2 (4.7)	0

Abbreviations: SAE = serious adverse event.
Note 1: Adverse events are coded using MedDRA Version 21.1.
Note 2: Treatment-emergent adverse events are defined as any adverse event that occurs after administration of the first dose of study drug and through 30 days after the last dose of study drug.
Note 3: Treatment-emergent adverse events occurring during the double-blind period are summarized by treatment arms.
Note 4: Patients are counted once for each preferred term. Incidence rates are based on the number of patients who initially received placebo or ripretinib 150 mg QD.
Note 5: Table cutoff based on either arm having ≥2% patients with an adverse event.
Source: NDA Module 2.5, Table 8

The Regulatory Authorities' Assessment:

FDA confirms the Applicant's analyses. Overall the incidence of SAEs was higher in the ripretinib arm than the placebo arm. When assessed at the HLGT level, the most common serious adverse event was gastrointestinal signs and symptoms occurring in 8% of the patients in the ripretinib arm and 4.7% of the patients in the placebo arm.

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:

During the double-blind period in, the TEAEs leading to treatment discontinuation in the ripretinib arm were reported in 7 (8.2%) patients and included general physical health deterioration (2 [2.4%]), anemia, cardiac failure, vomiting, death, and palmar-plantar erythrodysesthesia syndrome (1 [1.2%] patient each).

The TEAEs leading to treatment discontinuation in the placebo arm were reported in 5 (11.6%) patients. These included abdominal pain, gastrointestinal perforation, fatigue, genital herpes simplex, sepsis, pseudomonal urinary tract infection, facial bones fracture, blood creatinine increased, general physical condition decreased, confusional state, and acute kidney injury (1 [2.3%] patient each).

The Regulatory Authorities' Assessment:

The Regulatory Authorities agree with the Applicant's assessment.

Dose Interruption/Reduction Due to Adverse Effect

The Applicant's Position:

During the double-blind period in Study DCC-2618-03-001, there were 6 (7.1%) patients in the ripretinib arm and 1 (2.3%) patient in the placebo arm that had any TEAE leading to dose reduction. All TEAEs leading to dose reduction were reported in single patients in both arms.

In the ripretinib arm, TEAEs leading to dose reduction included abdominal pain, gastrointestinal disorder, weight decreased, arthritis, myalgia, hyperesthesia, agitation, alopecia, dermatosis, and palmar-plantar erythrodysesthesia syndrome (1 [1.2%] patient each).

In the placebo arm, TEAEs leading to dose reduction included a single case of diarrhea (1 [2.3%] patient).

Of the 85 patients in the ripretinib arm, any TEAE leading to dose interruption was reported in 20 (23.5%) patients. Of the 43 patients in the placebo arm, any TEAE leading dose interruption was reported 9 (20.9%) patients.

TEAEs leading to dose interruption reported in > 1 patient in the ripretinib arm included nausea (3 [3.5%]), blood bilirubin increased and palmar-plantar erythrodysesthesia syndrome (2 [2.4%] patients each).

All TEAEs leading to dose interruption were reported in single patients in the placebo arm and included anemia, small intestinal obstruction, asthenia, pyrexia, generalized edema, systemic inflammatory response syndrome, blood alkaline phosphatase increased, blood creatinine increased, gamma-glutamyltransferase increased, dehydration, tumor pain, renal failure, and hypotension.

The Regulatory Authorities' Assessment:

The Regulatory Authorities agree with the Applicant's assessment.

Significant Adverse Events

The Applicant's Position:

Adverse events of clinical importance (AECI) categories were selected based on the class effect, mechanism of action, and the clinical experience to date with ripretinib. These categories were used to evaluate the potential risks of ripretinib. The analysis of the AECIs was performed across the integrated dataset including all patients who received at least one dose of ripretinib in Studies DCC-2618-03-001 and DCC-2618-01-001 (Pool 3).

The most common AECIs (reported in ≥ 25% of total patients) were alopecia (49.6% [174/351]), myalgia (36.2% [127/351]), palmar-plantar erythrodysesthesia syndrome (28.8% [101/351]), and diarrhea (26.8% [94/351]). Notably, alopecia was the most commonly reported TEAE. Myalgia and arthralgia were other events considered expected with ripretinib treatment; arthralgia was observed in 18.2% (64/351) of total patients.

The most common Grade 3/4 AECIs (reported in >1 patient) were hypertension (6.6% [23/351]); blood bilirubin increased (2.0% [7/351]); diarrhea (1.4% [5/351]); edema peripheral (0.9% [3/351]); and hyperbilirubinemia and cardiac failure (0.6% [2/351] in each). All other Grade 3/4 AECIs were reported in a single patient.

All other serious AECIs were reported in a single patient. No SAEs of myalgia or palmar-plantar erythrodysesthesia syndrome were reported.

An SAE of Grade 3 Stevens-Johnson syndrome was observed in 1 patient 10 days following the initiation of ripretinib. After a positive re-challenge at a reduced dose, the study treatment was permanently discontinued due to the SAE and was considered by the investigator to be definitely related to ripretinib. The patient was not hospitalized for this event and the SAE resolved on Day 51 of the study.

The Regulatory Authorities' Assessment:

FDA's assessment of AECIs is provided in Section 8.2.5.

Treatment Emergent Adverse Events and Adverse Reactions

The Applicant's Position:

A summary of TEAEs in each treatment arm is presented in Table 20. For any TEAE, the treatment arms are comparable: 84 (98.8%) of 85 patients and 42 (97.7%) of 43 patients experienced a TEAE in the ripretinib arm and the placebo arm, respectively.

TEAEs occurring in ≥ 20% of patients in the ripretinib arm (in decreasing order of frequency) by PT included alopecia (44 [51.8%]), fatigue (36 [42.4%]), nausea (33 [38.8%]), abdominal pain (31 [36.5%]), constipation (29 [34.1%]), myalgia (27 [31.85%]), diarrhea (24 [28.2%]), decreased appetite (23 [27.1%]), palmar-plantar erythrodysesthesia syndrome (18 [21.2%]), and vomiting (18 [21.2%]).

TEAEs occurring in ≥ 20% of patients in in the placebo arm (in decreasing order of frequency) by PT included abdominal pain (13 [30.2%]), fatigue (10 [23.3%]), and decreased appetite (9 [20.9%]). In the placebo arm, there were no TEAEs of palmar-plantar erythrodysesthesia syndrome, blood bilirubin increased, dyspnea, hypophosphatemia, lipase increased, or stomatitis reported.

Table 20: Treatment-emergent Adverse Events Experienced in ≥ 10% Patients by Preferred Term in Double-blind Period (Safety Population)

Preferred Term	Placebo (N = 43) n (%)	Ripretinib (N = 85) n (%)
Any Event	42 (97.7)	84 (98.8)
Alopecia	2 (4.7)	44 (51.8)
Fatigue	10 (23.3)	36 (42.4)
Nausea	5 (11.6)	33 (38.8)
Abdominal pain	13 (30.2)	31 (36.5)
Constipation	8 (18.6)	29 (34.1)
Myalgia	5 (11.6)	27 (31.8)
Diarrhoea	6 (14.0)	24 (28.2)
Decreased appetite	9 (20.9)	23 (27.1)
Palmar-plantar erythrodysaesthesia syndrome	0	18 (21.2)
Vomiting	3 (7.0)	18 (21.2)
Headache	2 (4.7)	16 (18.8)
Weight decreased	5 (11.6)	16 (18.8)
Arthralgia	2 (4.7)	15 (17.6)
Blood bilirubin increased	0	14 (16.5)
Oedema peripheral	3 (7.0)	14 (16.5)
Muscle spasms	2 (4.7)	13 (15.3)
Anaemia	8 (18.6)	12 (14.1)

Preferred Term	Placebo (N = 43) n (%)	Ripretinib (N = 85) n (%)
Hypertension	2 (4.7)	12 (14.1)
Asthenia	6 (14.0)	11 (12.9)
Dry skin	3 (7.0)	11 (12.9)
Dyspnoea	0	11 (12.9)
Hypophosphataemia	0	9 (10.6)
Lipase increased	0	9 (10.6)
Pruritus	2 (4.7)	9 (10.6)
Stomatitis	0	9 (10.6)
Insomnia	6 (14.0)	8 (9.4)
Dyspepsia	6 (14.0)	7 (8.2)
Abdominal distension	5 (11.6)	3 (3.5)

Note 1: Adverse events are coded using MedDRA Version 21.1.
Note 2: Treatment-emergent adverse events are defined as any adverse event that occurs after administration of the first dose of study drug and through 30 days after the last dose of study drug.
Note 3: Treatment-emergent adverse events occurring during the double-blind treatment period are summarized by treatment arms.
Note 4: Patients are counted once for each preferred term. Incidence rates are based on the number of patients who initially received placebo or ripretinib 150 mg QD.
Note 5: Table cutoff based on either arm having ≥ 10% patients with an adverse event.
Source: NDA Module 2.5, Table 6

Table 21 summarizes Grade 3 or 4 TEAEs in each treatment arm that occurred during the double-blind period of Study DCC-2618-03-001.

In the ripretinib arm, 42 (49.4%) patients experienced any Grade 3/4 event. The most commonly reported Grade 3/4 events experienced in ≥ 5% patients were anemia (8 [9.4%]), abdominal pain and hypertension (6 [7.1%]) patients each).

In the placebo arm, 19 (44.2%) patients experienced any Grade 3/4 event. The most commonly reported Grade 3/4 event shown in ≥ 5% patients was anemia (6 [14.0%]).

Table 21: Grade 3/4 Treatment-emergent Adverse Events Reported by ≥ 2 Patients by Preferred Term in Double-blind Period (Safety Population)

Preferred Term	Placebo (N = 43) n (%)	Ripretinib (N = 85) n (%)
Any Grade 3/4 Event	19 (44.2)	42 (49.4)
Anaemia	6 (14.0)	8 (9.4)
Abdominal pain	2 (4.7)	6 (7.1)
Hypertension	0	6 (7.1)
Hypophosphataemia	0	4 (4.7)
Lipase increased	0	4 (4.7)
Blood alkaline phosphatase increased	1 (2.3)	3 (3.5)
Fatigue	1 (2.3)	3 (3.5)
Nausea	0	3 (3.5)
Vomiting	0	3 (3.5)
Acute kidney injury	1 (2.3)	2 (2.4)
Ascites	0	2 (2.4)
Aspartate aminotransferase increased	1 (2.3)	2 (2.4)
Dehydration	1 (2.3)	2 (2.4)
Urinary tract infection	1 (2.3)	2 (2.4)
Asthenia	2 (4.7)	1 (1.2)
Gamma-glutamyltransferase increased	2 (4.7)	1 (1.2)
Sepsis	2 (4.7)	1 (1.2)

Note 1: Adverse events are coded using MedDRA Version 21.1.
Note 2: Treatment-emergent adverse events are defined as any adverse event that occurs after administration of the first dose of study drug and through 30 days after the last dose of study drug.
Note 3: Treatment-emergent adverse events occurring during the double-blind treatment period are summarized by treatment arms.
Note 4: One treatment-emergent "FEVER" which misses severity grade is summarized as Grade 3 ("severe"). (Patient (b) (6))
Note 5: Patients are counted once for each preferred term. Incidence rates are based on the number of patients who initially received placebo or ripretinib 150 mg QD.
Note 6: Table cutoff based on either arm having ≥ 2 patients with an adverse event.
Source: NDA Module 2.5, Table 7

The Regulatory Authorities' Assessment:

FDA confirms the Applicant's analyses of TEAEs at the PT level. FDA additionally analyzed the frequency of adverse events at all levels of the MedDRA hierarchy. As expected, the assessment of many of the more commonly occurring adverse events using grouped PTs demonstrated higher frequencies. For example, at the PT level, the frequency of abdominal pain in the ripretinib arm was 37%, while at the level of HLGT, the frequency of gastrointestinal and abdominal pains (excl. oral and throat), which includes the PTs abdominal pain, abdominal pain lower, and abdominal pain upper, was 44%. The most commonly occurring TEAE during the double-blinded period at the HLT level and SOC level, respectively, are shown in tables below. Analysis of all MedDRA levels did not identify any safety signals beyond those identified at the PT level.

Table 21.1. Most Common (≥ 20%) Treatment-emergent Adverse Events by Higher Level Term in Double-blind Period in Study DCC-2618-03-001

Higher Level Term (HLT)	Ripretinib (N = 85) n (%)	Placebo (N = 43) n (%)
Asthenic Conditions	47 (55)	16 (37)
Alopecias	44 (52)	2 (4.7)
Gastrointestinal and abdominal pains (excl oral and throat)	37 (44)	16 (37)
Nausea and vomiting symptoms	37 (44)	8 (19)
Gastrointestinal atonic and hypomobility disorders NEC	30 (35)	9 (21)
Muscle pains	27 (32)	5 (12)
Diarrhea (excl infective)	24 (28)	6 (14)
Musculoskeletal and connective tissue pain and discomfort	24 (28)	7 (16)
Appetite disorders	(23 (27)	9 (21)
Dermal and epidermal conditions NEC	20 (24)	3 (7)
Dermatitis ascribed to specific agent	18 (21)	0
Physical examination procedures and organ system status	18 (21)	6 (14)
Liver function analysis	18 (21)	3 (7)

Source: Reviewer table based on DCC-2618-03-001: ADAE dataset

Table 21.2. Most Common (≥ 40%) Treatment-emergent Adverse Events by SOC in Double-blind Period in Study DCC-2618-03-001

SOC	Ripretinib (N = 85) n (%)	Placebo (N = 43) n (%)
Gastrointestinal disorders	71 (84)	33 (77)
General disorders and administration site conditions	58 (68)	21 (49)
Skin and subcutaneous tissue disorders	58 (68)	8 (19)
Musculoskeletal and connective tissue disorders	49 (58)	13 (30)
Metabolism and nutrition disorders	39 (46)	12 (28)

Source: Reviewer table based on DCC-2618-03-001: ADAE dataset

Laboratory Findings

The Applicant's Position:

Abnormal chemistry and hematology results are based on the known side effect profile of ripretinib and potential class effects.

The Regulatory Authorities' Assessment:

The table below summarizes the incidence of treatment emergent laboratory abnormalities occurring in the safety population during the double blinded period. There were no Grade 4 laboratory abnormalities reported for any tested parameter on either the ripretinib or the placebo arm.

The incidence of Grades 1-3 laboratory abnormalities was ≥ 5 % higher in the ripretinib arm compared to the placebo arm for the following parameters: decreased neutrophils, decreased platelets, decreased white blood cells, increased lipase, decreased phosphorous, decreased calcium, increased creatine kinase, increased bilirubin, decreased sodium, increased amylase, decreased potassium, increased magnesium, and increased APTT.

The incidence of Grade 3 laboratory abnormalities was ≥ 5% higher in the ripretinib arm only for the parameter decreased phosphorous where the incidence of any Grade was 26% in the ripretinib arm and 2.5% in the placebo arm and the incidence of Grade 3 abnormalities was 4.8% in the ripretinib arm compared to 0 in the placebo arm.

Table 21.3. Study DCC-2618-03-001: Incidence of Treatment-Emergent Laboratory abnormalities Occurring in ≥ 5% or ≥ 2% Grade 3 with Ripretinib during Double-Blinded Period

Parameter	Ripretinib			Placebo		
	N[1]	Any Grade %	Grade 3[2] %	N[1]	Any Grade %	Grade 3[2] %
Hematology						
Decreased Hemoglobin	84	52	4.8	40	78	15
Decreased Lymphocytes	84	25	3.6	40	25	5
Decreased Neutrophils	84	11	0	40	2.5	0
Decreased Platelets	84	8	0	40	0	0
Decreased White Blood Cells	84	7	0	40	0	0
Serum Chemistry						
Increased Triglycerides	84	45	2.4	40	40	0
Increased Lipase	84	32	8	40	15	7.5
Increased Alkaline Phosphatase	84	31	2.4	40	37.5	7.5
Increased Creatinine	84	27	0	40	37.5	0
Decreased Phosphorus	84	26	4.8	40	2.5	0
Decreased Calcium	84	25	0	40	10	0
Increased Creatine Kinase	84	24	1.2	40	10	0
Increased AST	84	23	2.4	40	20	2.5
Decreased Magnesium	84	21	0	40	25	0
Increased Bilirubin	84	21	0	40	5	2.5
Decreased Sodium	84	20	2.4	40	10	2.5
Increased Amylase	84	18	1.2	40	7.5	0
Increased ALT	84	14	1.2	40	15	0
Increased Potassium	84	13	6	39	13	5
Decreased Albumin	84	12	1.2	40	17.5	0
Decreased Potassium	84	12	2.4	39	8	0
Increased Magnesium	84	8	0	40	0	0
Coagulation						
Increased APTT	81	42	0	34	15	0
Increased INR	81	23	3.7	34	21	0

Source: Reviewer table based on ADLB dataset

[1] N = number of patients with baseline value and at least 1 post baseline assessment for the parameter.

[2] No grade 4 laboratory abnormalities were reported in the assessed dataset.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; APTT = activated partial thromboplastin time; INR = international normalized ratio

Vital Signs

The Applicant's Position:

Blood Pressure

Integrated analyses were performed for blood pressure. A total of 77.5% (272/351) of patients in Pool 3 had a systolic blood pressure within normal range (<140 mmHg), and 91.7% (322/351) of patients had a diastolic blood pressure within normal range (<90 mmHg) at baseline. The mean (SD) baseline systolic and diastolic blood pressure for all patients was 128.0 (15.75) and 74.2 (10.82) mmHg, respectively. Though the average baseline blood pressure for all treated patients was within normal range, most patients reported having a past medical history of high blood pressure prior to starting ripretinib, with hypertension being reported in the medical history of 56.1% (197/351) of total patients at baseline.

Although patients did experience an increase in systolic and diastolic blood pressure from baseline, most evaluable patients (43.9% [154/351]) experienced no shift in post-baseline systolic blood pressure, and the majority (62.7% [220/351]) experienced no shift in post-baseline diastolic blood pressure. Only 3.4% [12/351]) of patients who were within normal range at baseline had a post-baseline systolic blood pressure ≥ 160 mmHg, and 2.0% (7/351) of patients who had a normal diastolic blood pressure at baseline had a post-baseline value ≥ 100 mmHg.

Across Pool 3, hypertension was reported as an AE in 59 of 351(16.8%) patients; of these, 23 patients experienced a Grade 3/4 TEAE of hypertension. Blood pressure increased was reported as an AE in 0.9% ([3/351]) of patients. Sixteen (4.6%) patients had an AE of hypotension, and no patient had an AE of blood pressure decreased.

The Regulatory Authorities' Assessment:

FDA analyzed changes in weight and blood pressure that occurred during the double blinded period of the DCC-2618-03-001 trial for all patients who received at last one dose of study drug.

Weight: A weight loss of ≥ 5% was reported in 40/85 (47%) of patients in the ripretinib arm compared to 8/43 (19%) of patients in the placebo arm. The mean decrease in weight for patients in the ripretinib arm was -8.9% (SD 4.2) with a median decrease of -7.4% (-5% to 23%) The higher proportion of patients in the ripretinib arm who experienced weight loss may reflect longer exposure time for patients in that arm and/or the higher incidence of gastrointestinal related adverse events compared to placebo.

Blood Pressure: The table below shows maximum shift in hypertension (diastolic and/or systolic) by CTCAE 4.03 grading from baseline reported during the double blinded period by arm for patients who received at least one dose of study drug. The distribution of baseline

hypertension grades was similar between the arms. Entries representing at least one increase in hypertension grade from baseline are shown in bold. In the ripretinib arm, 38 patients (45%) experienced at least one grade increase from baseline, with most being only one grade increase compared to 20 (50%) in the placebo arm. The percentage of patients with maximum Grade 2 (35% versus 30%) and maximum Grade 3 (13% versus 10%) regardless of baseline was similar between arm.

Table 21.4. Shift Table for Maximum Grade Hypertension[1] from Baseline Grade Hypertension during Double-Blinded Period in Study DCC-2618-03-001

	Baseline	N (%)	Grade 0	Grade 1	Grade 2	Grade 3
Ripretinib	0	27 (32)	5	**15**	**7**	**0**
	1	35 (42)	3	16	**13**	**3**
	2	17 (20)	0	5	6	**6**
	3	5 (6)	0	0	3	2
Total Any baseline		84	8	36	29	11
Placebo	0	13 (33)	4	**8**	**1**	**0**
	1	18 (45)	1	9	**7**	**1**
	2	8 (20)	0	1	4	**3**
	3	1 (3)	0	1	0	0
Total Any Baseline		40	5	19	12	4

Source: Reviewer table based on DCC-2618-03-001: ADVS dataset.
[1] Hypertension Grading (CTCAE V4.03) Grade 0 (normotensive): systolic BP < 120 mm Hg and diastolic BP < 80 mm Hg; Grade 1: systolic BP 120-139 mm Hg and/or diastolic BP 80-89 mm Hg; Grade 2: systolic BP 140-159 mm Hg and/or diastolic BP 90-99 mm Hg; Grade 3: systolic BP ≥ 160 mm Hg and/or diastolic ≥ 100 mmHg.
[2] Number of patients with baseline grade and at least one post baseline measurement.

Electrocardiograms (ECGs)/ QT Prolongation

The Applicant's Position:

In Study DCC-2618-01-001, ECGs were assessed to investigate the effect of ripretinib on cardiac repolarization, heart rate (HR), PR, QRS, QT intervals, and T-wave morphology. Ripretinib in daily doses between 40 mg (20 mg BID) and 400 mg (200 mg BID) did not have a clinically relevant effect on ECG parameters. An effect on the QTcF interval exceeding 10 ms can be

excluded within the observed range of plasma concentrations for both ripretinib and the metabolite DP-5439.

An analysis of QTc prolongation and a search for AEs of Torsades de Pointes, as requested by the FDA was conducted. The AE data provided is not suggestive of drug-induced QT prolongation or Torsades de Pointes.

The Regulatory Authorities' Assessment:

The Interdisciplinary Review Team for Cardiac Safety Studies performed a full consultation and submitted a separate report. For the consultation, the effect of ripretinib was evaluated in the dose-ranging study DCC-2618-01-001. As stated in the report, the primary analysis, which used an exposure-response analysis, did not suggest that ripretinib is associated with large mean increases in the QTc interval. The findings were further supported by trends observed in the by-time analysis and the categorical analysis. In summary, the reports states that no large mean increases in the QTc interval (i.e., 20 msec) were observed for the therapeutic dose of 150 mg QD ripretinib; however, in the absence of a positive control or a large exposure margin above therapeutic exposure, there is reluctance to draw conclusion for a lack of a QT effect for ripretinib.

Immunogenicity

The Applicant's Position:

Not applicable

The Regulatory Authorities' Assessment:

Not applicable.

8.2.5. Analysis of Submission-Specific Safety Issues

The Applicant's Position:
As described in Section 8.2.1, adverse events of clinical importance (AECI) categories were selected based on the class effect, mechanism of action, and the clinical experience to date with ripretinib. These categories were used to evaluate the potential risks of ripretinib and are presented in Table 18.

The most common AECIs (reported in ≥ 25% of total patients) were alopecia (49.6% [174/351]), myalgia (36.2% [127/351]), palmar-plantar erythrodysesthesia syndrome (28.8% [101/351]),

and diarrhea (26.8% [94/351]) (Table 22). Notably, alopecia was the most commonly reported TEAE in this study and is considered of clinical importance. A total of 55.0% (164/298) of patients with GIST had at least 1 event of alopecia. All TEAEs of alopecia were described as mild (Grade 1) and moderate (Grade 2) in severity. Of the 164 patients with alopecia, 1 (0.3%) patient had an event of alopecia that required dose reduction; 1 (0.3%) patient had an event of alopecia that resulted in dose interruption; and no patients in Study DCC-2618-01-001 had an event of alopecia that led to discontinuation from the study. Myalgia and arthralgia were other events considered expected with ripretinib treatment; arthralgia was observed in 18.2% (64/351) of total patients.

Table 22: Treatment-Emergent Adverse Events of Clinical Importance by SMQ/CMQ, Preferred Term, and Disease Group in Pool 3 (Safety Population)

Category Preferred Term	GIST (N = 298) n (%)	Non-GIST (N = 53) n (%)	Total (N = 351) n (%)
Cardiac Failure	46 (15.4)	2 (3.8)	48 (13.7)
Oedema peripheral	39 (13.1)	1 (1.9)	40 (11.4)
Peripheral swelling	4 (1.3)	0	4 (1.1)
Cardiac failure	3 (1.0)	0	3 (0.9)
Acute left ventricular failure	1 (0.3)	0	1 (0.3)
Diastolic dysfunction	0	1 (1.9)	1 (0.3)
Ejection fraction decreased	1 (0.3)	0	1 (0.3)
Orthopnoea	1 (0.3)	0	1 (0.3)
Pulmonary oedema	1 (0.3)	0	1 (0.3)
Hypertension	57 (19.1)	4 (7.5)	61 (17.4)
Hypertension	57 (19.1)	2 (3.8)	59 (16.8)
Blood pressure increased	1 (0.3)	2 (3.8)	3 (0.9)
Diarrhea	91 (30.5)	8 (15.1)	99 (28.2)
Diarrhoea	87 (29.2)	7 (13.2)	94 (26.8)
Abdominal infection	1 (0.3)	1 (1.9)	2 (0.6)
Anal abscess	1 (0.3)	0	1 (0.3)
Bacterial abdominal infection	1 (0.3)	0	1 (0.3)
Campylobacter gastroenteritis	0	1 (1.9)	1 (0.3)
Enterocolitis infectious	1 (0.3)	0	1 (0.3)

Category Preferred Term	GIST (N = 298) n (%)	Non-GIST (N = 53) n (%)	Total (N = 351) n (%)
Gastric infection	1 (0.3)	0	1 (0.3)
Gastroenteritis	1 (0.3)	0	1 (0.3)
Gastroenteritis viral	1 (0.3)	0	1 (0.3)
Arthralgia	63 (21.1)	3 (5.7)	66 (18.8)
Arthralgia	61 (20.5)	3 (5.7)	64 (18.2)
Joint range of motion decreased	1 (0.3)	0	1 (0.3)
Joint stiffness	1 (0.3)	0	1 (0.3)
Joint swelling	1 (0.3)	0	1 (0.3)
Myalgia	121 (40.6)	6 (11.3)	127 (36.2)
Myalgia	121 (40.6)	6 (11.3)	127 (36.2)
Hand Foot Syndrome	118 (39.6)	5 (9.4)	123 (35.0)
Palmar-plantar erythrodysaesthesia syndrome	98 (32.9)	3 (5.7)	101 (28.8)
Pain of skin	12 (4.0)	0	12 (3.4)
Paraesthesia	10 (3.4)	1 (1.9)	11 (3.1)
Hyperaesthesia	4 (1.3)	1 (1.9)	5 (1.4)
Neurodermatitis	2 (0.7)	1 (1.9)	3 (0.9)
Dysaesthesia	2 (0.7)	0	2 (0.6)
Palmoplantar keratoderma	2 (0.7)	0	2 (0.6)
Palmar erythema	1 (0.3)	0	1 (0.3)
Skin burning sensation	1 (0.3)	0	1 (0.3)
Alopecia	164 (55.0)	10 (18.9)	174 (49.6)
Alopecia	164 (55.0)	10 (18.9)	174 (49.6)
Actinic Keratosis, SCC of skin	50 (16.8)	6 (11.3)	56 (16.0)
Actinic keratosis	32 (10.7)	3 (5.7)	35 (10.0)
Squamous cell carcinoma of skin	13 (4.4)	3 (5.7)	16 (4.6)
Keratoacanthoma	6 (2.0)	1 (1.9)	7 (2.0)

Category Preferred Term	GIST (N = 298) n (%)	Non-GIST (N = 53) n (%)	Total (N = 351) n (%)
Basal cell carcinoma	4 (1.3)	1 (1.9)	5 (1.4)
Malignant melanoma in situ	2 (0.7)	0	2 (0.6)
Squamous cell carcinoma	2 (0.7)	0	2 (0.6)
Bowen's disease	1 (0.3)	0	1 (0.3)
Dysplastic naevus	1 (0.3)	0	1 (0.3)
Malignant melanoma	1 (0.3)	0	1 (0.3)
Stevens-Johnson Syndrome	1 (0.3)	1 (1.9)	2 (0.6)
Erythema multiforme	0	1 (1.9)	1 (0.3)
Stevens-Johnson syndrome	1 (0.3)	0	1 (0.3)
Hyperbilirubinemia	53 (17.8)	8 (15.1)	61 (17.4)
Blood bilirubin increased	40 (13.4)	6 (11.3)	46 (13.1)
Hyperbilirubinaemia	14 (4.7)	3 (5.7)	17 (4.8)
Jaundice	2 (0.7)	0	2 (0.6)

Abbreviations: GIST = gastrointestinal stromal tumor; MedDRA = Medical Dictionary for Regulatory Activities; "Non-GIST" group includes patients with other advanced malignancies than GIST; SMQ = Standardized MedDRA queries; CMQ = customized MedDRA queries.
Note 1: Adverse events were coded with MedDRA dictionary v21.1.
Note 2: Treatment-emergent adverse events are defined as any adverse event that occurs after administration of the first dose of ripretinib and through 30 days after the last dose of ripretinib and any event considered as drug-related by the Investigator.
Note 3: Patients who have more than 1 adverse event per preferred term are counted only once in each term.
Data cut-off date for study DCC-2618-01-001: 01 March 2019.
Data cut-off date for study DCC-2618-03-001: 31 May 2019.
Source: NDA Module 2.7.4, Table 27

The most common Grade 3 or 4 AECIs (occurring in ≥ 2 patients) were hypertension (6.6% [23/351]); blood bilirubin increased (2.0% [7/351]); diarrhea (1.4% [5/351]); edema peripheral (0.9% [3/351]); and hyperbilirubinemia and cardiac failure (0.6% [2/351] in each). All other Grade ¾ AECIs were reported in a single patient.

The Regulatory Authorities' Assessment:

Adverse Events of Clinical Importance

FDA is able to reproduce the results shown in Table 22 using the ISS.ADAE dataset and variables POOL3FL, TRETEMFL, ATOXGR, AECIFL, CFFL, HTNGL, DFL, ARFL, MYFL, HFSFL, AFL, SPCFL, SHSFL, HFL.

FDA's assessment of AECI is based primarily on the safety data from the double-blinded period of Study DCC-2618-03-001 and the ISS comprising 351 patients with a diagnosis of advanced solid tumor who received at least one dose of ripretinib.

- Cardiac Toxicities

  Cardiac Failure
  The PT cardiac failure is reported in one patient in the ripretinib arm (1.2%) compared to no patients in the placebo arm. Analysis using a grouped term cardiac failure (comprising the PTs acute left ventricular failure, cardiac failure, diastolic dysfunction, and ventricular hypertrophy) identified no additional cases in the ripretinib arm or placebo arm. Inclusion of adverse events occurring outside the double blinded period on Study DCC-2618-03-001 did not identify any additional cases. Search for treatment emergent events of the grouped term cardiac failure in the patients enrolled on DCC-2618-01-001 identified 6 events in 5 patients. Thus, the overall frequency of cardiac failure events in the ISS is 1.7% (6/351), including Grade 3 events in 4 patients (1.1%).

  The table below summarizes the narratives for these cases. Based on the narratives, the Reviewer assesses the events as at least possibly related to ripretinib in all 6 cases.

Narrative Summaries for Patients with Adverse Event of Cardiac Failure/ Dysfunction

DCC-2618-03-001	
SubjectID: (b) (6) **PT:** Cardiac failure **Grade:** 3 **Study Day**: 105 **Dosage:** 150 mg QD **Reviewer Assessment:** Possibly related	The patient is a 56 year old female with a diagnosis of Stage IV GIST with medical history significant for ongoing hyperlipidemia, hypertension and hypertrophic cardiomyopathy. Echocardiogram at screening showed a left ventricular ejection fraction of 60%. On day 105, the patient presented with progressive shortness of breath over the past 2 months. Troponin-I was within reference range (0.03 ng/mL) and BNP was elevated at 3671.9 pg/mL (ULN 75.5). On day 106, an echocardiogram showed an LVEF of 25% to 30%. Ripretinib was discontinued due to cardiac failure. On day 108, LVEF was 31%. Dobutamine stress test results included abnormal myocardial perfusion with an anterior and apical reversible defect indicative of ischemia and a gated wall motion analysis with LVEF of 42%. Repeat echocardiogram on day 133 showed an LVEF of 39%. Day 176, LVEF as 150%, troponin I was within reference range. BNP remained elevated at 497 ug/L (ULN 150). The Applicant assessed the SAE as cardiac failure as possibly related to ripretinib. The reviewer concurs.
DCC-2618-01-001	
SubjectID: (b) (6) **PT:** Acute Left ventricular Failure **Grade:** 3 **Study Day**: **Dosage:** 150 mg BID **Reviewer Assessment:** Possibly related	The patient is a 78 year old male with a diagnosis of Stage IV GIST and medical history significant for atrial fibrillation, dyspnea exertional, and hypertension. On Study Day 260, an echocardiogram showed a decreased LVEF of 31%. At screening LVEF was 55% and approximately 3 months prior to the event was 40%. On day 263, the patient presented to the ER with 4 day history of worsening dyspnea, dyspnea upon exertion, orthopnea, generalized weakness. In the ER the patient was found to have tachycardia and lower extremity weakness. Laboratory assessment showed elevated white blood cell count and neutrophils, decreased hemoglobin along with elevated AST, ALT, NG-proBNP antibodies, troponin I, and lactic acid. Echocardiogram showed severely reduced LVEF of 10% and was diagnosed with acute on chronic systolic congestive heart failure. The Applicant assessed the event as not related to treatment with study drug. The reviewer does not agree and finds the progressive decreased in LVEF while on study to be at least possibly related to ripretinib.

SubjectID: (b) (6) **PT:** Cardiac failure **Grade:** 2 **Study Day**: **Dosage:** 100 mg QD **Reviewer Assessment:** Possibly related	The patient is a 64 year old male with a diagnosis of Stage IV GIST and medical history significant for hypertension, hyperlipidemia, and hypothyroidism. On Study Day 428, the patient experienced the SAE of cardiac failure. The LVEF was 41% with prior LVEF above 50%. On study day 434, cardiac catherization identified mode to moderate 2-vessel CAD with post procedure diagnosis of no ischemic cardiomyopathy. It was noted that this would not explain the severity of the LV dysfunction. On day 456, the patient's LVEF remained decreased at 41%. The Sponsor assessed the event of cardiac failure as possibly related to study treatment. The reviewer agrees.
SubjectID: (b) (6) **PT:** Cardiac failure, **SubjectID:** Grade 3 **Study Day**: 309 **Dosage: 150** mg QD **Reviewer Assessment:** Possibly related	The patient is a 72 year old male with a diagnosis of Stage IV GIST with medical history significant for ongoing coronary artery disease, hypercholesterolemia, and hypertension. The screening echocardiogram was 58%. The patient initiated treatment at a dosage of 150 mg QD. After approximately 2 months, the patient increased the dose to 150 mg BID. Approximately 8 months after increasing the dose (day 309), the patient presented to the emergency center with cough and abdominal pain and was hospitalized for cardiac failure. Study day 310, an Echocardiogram showed an LVEF of 29%. Subsequent angiogram showed diffused moderate coronary artery disease, congestive heart failure NYHA class II-III, 30% ostial stenosis in the proximal left main coronary artery, and 50% stenosis in the proximal left anterior descending artery. Approximately 1 month after presenting with cardiac failure, the LVEF was 37%. The Applicant assessed the event as possibly related to study drug. The reviewer concurs.
SubjectID: (b) (6) **PT:** Diastolic dysfunction (x 2) **Grade:** 3 **Study Day**: 14 and 85: **Dosage:** 150 mg QD, 100 mg QD **Reviewer Assessment:** Possibly related	Patient is an 86 year old male with a diagnosis of malignant melanoma and medical history significant for ongoing hypertension, coronary artery disease, and bradycardia. On Study Day 15, the patient presented to the emergency department with shortness of breath and was hospitalized for diastolic dysfunction. Echocardiogram showed diastolic dysfunction with preserved ejection fraction. The patient was treated with furosemide and felt better. The adverse event of diastolic dysfunction was reported as recovered/recovered on the same day. The patient was restarted on study drug at a lower dose. On Day 85, the event of diastolic dysfunction (Grade 3) was reported again and study drug was discontinued. The Applicant assessed the second occurrence of diastolic dysfunction as possibly related to ripretinib. The reviewer concurs.

SubjectID: (b) (6) **PT:** Ventricular hypertrophy **Grade:** 1 **Study Day**: **Dosage:** 150 mg QD **Reviewer Assessment:** Probably related	The patient is a 55 year old male with a diagnosis of Stage IV GIST and medical history significant for hypertension and ventricular arrythmia. On Study Day 42, transthoracic echocardiogram showed mild hypertrophy with an ejection fraction of 71%. There was mild to moderate left atrial enlargement. On Day 141, the patient experienced the SAE left ventricular outflow tract obstruction. ECHO at that time showed a LVEF of 74% with hypertrophic obstructive physiology. The patient was found to have new onset hyperthyroidism but without tachypnea or other signs and symptoms. The drug was withdrawn on Day 142. On Day 146, the patient reported significant symptomatic improvement in breathing exercise intolerance. A repeat transthoracic ECHO showed reversal of the left ventricle outflow tract obstruction with LVEF of 67%. The Sponsor assessed the SAE of left ventricle outflow tract obstruction as possible related to study drug. The reviewer assesses it as probably related given the resolution after discontinuation of study drug.

Analysis of data from echocardiogram studies provides another means of evaluating the potential impact of ripretinib on cardiac function. The table below summarizes the results of such an analysis. As seen in the population characteristics, the baseline LVEF for patients in the ripretinib arm is similar to that for patients in the placebo arm. A decrease in LVEF to ≤ 40% is rare with, in the ripretinib arm, only 1 patient (1.3%) having a drop in LVEF to 40-49% and 1 patient (1.3%) having a drop to ≤ 30. No patient in the placebo arm had a decrease in LVEF to < 50%. If the percent change from baseline is considered, the frequency of a -10 to -19% change is similar between the ripretinib and placebo arm with 2 patients in the ripretinib arm having a ≥ -20 change (2.6%) but no patients in the placebo experienced such a change.

Patients in the ISS had mean and median baseline LVEF similar to patients in the ripretinib and placebo arms. Mean and median post-baseline were also similar. The frequency of minimum post baseline LVEF ≤ 30 is similar between the ripretinib arm and ISS but one patient had a drop to < 30 (0.4%) and 3 patients in the ISS (1.1%) had a percent change in LVEF ≥ -40.

In the ripretinib arm, 2.3% of patients (2/77) had a decrease in LVEF to < 50 with an absolute decrease of at least 10%, while no patient the placebo arm had similar decrease in cardiac function. The two patient had Grade 3 ejection fraction decrease. In the ISS, 3.4% of patients (9/261) had a decrease in LVEF to < 50 with an absolute decrease of at least 10%. All 9 patients had Grade 3 ejection fraction decrease.

Table 22.1. Changes in Left Ventricular Ejection Fraction DCC-2618-03-001 Double Blinded Period and ISS

	DCC-2618-03-001 Double Blinded Period		ISS
	Ripretinib N=77	Placebo N=22	N=261
Population Characteristics			
Mean Baseline LVEF -- % (SD)	62.9 (6.3)	63.3 (5.9)	62.6 (5.6)
Median Baseline LVEF -- % (min, max)	63 (50,82)	63 (55, 81)	63 (50,82)
Mean Minimum Post-baseline LVEF -- % (SD)	62 (7.6)	62 (30,82)	61.1 (7.0)
Median Minimum Post-baseline LVEF % (SD)	63 (4.8)	64 (55, 74)	62 (29, 84)
Frequency of Decreased LVEF n (%)			
Minimum LVEF 40 - 49	1 (1.3)	0	6 (2.3)
Minimum LVEF 30 - 39	1 (1.3)	0	3 (1.1)
Minimum LVEF < 30	0	0	1 (0.4)
Percent Change (decrease) 10 - 19	7 (9)	3 (14)	32 (11)
Percent Change (decrease) 20-29	1 (1.3)	0	5 (1.9)
Percent Change (decrease) 30-39	1 (1.3)	0	1 (0.4)
Percent Change (decrease) ≥ 40	0	0	3 (1.1)
CTCAE Grade Ejection Fraction Decrease*			
Grade 3	2 (2.6)	0	9 (3.4)
Grade 4	0	0	0

Source: Reviewer table based on DCC-2618-03-001: ADECHO and ISS: ADECHO
* Grade 3: LVEF 39%-20% or > 20% drop from baseline; Grade 4 LVEF < 20%

Since the majority of cases of decreased cardiac function identified through adverse event reporting occurred in patients enrolled on DCC-2618-03-001, a separate analysis of the ISS by study was performed. This analysis did not identify any differences in baseline LVEF or minimum post-baseline LVEF. Despite this, the frequency of patients with minimum post-baseline LVEF < 50% was higher in patients enrolled on DCC-2618-03-001 (4.5%) compared to patients enrolled on DCC-2618-03-001 who received at least 1 dose of ripretinib (2.8%), and a higher percentage of patients enrolled on DCC-2618-01-001 had a percent change in LVEF ≥ - 20% (3.8%) compared to patients enrolled on DCC_2618-03-001 who received at least one dose of ripretinib (2.8%). These differences may be due to chance or may indicate that patients enrolled on DCC-2618-01-001 were at higher risk of developing cardiac dysfunction despite having similar baseline LVEF characteristics.

While a definitive causal relationship cannot be concluded between events of cardiac dysfunction, based on the adverse event reporting, there is sufficient information to suggest

ripretinib may, in rare cases, contribute to a decrease in cardiac function. This potential risk should be included in Warnings and Precautions (Section 5) in the label.

Cardiac Ischemic Events
Search for treatment emergent events using a group term cardiac ischemic events (comprising the PTs acute coronary syndrome, acute myocardial infarction, cardiac arrest, and myocardial infarction) did not retrieve any cases occurring on Study DCC-2618-03-001. Search of patients enrolled on DCC-2618-01-001 identified 5 events in 4 patients. Thus, the overall frequency of treatment emergent cardiac ischemic events the ISS is 1.1% (4/351), including 2 fatal events.

The table below summarizes the narratives for these 4 cases. Based on the narratives, the Reviewer assesses the events as at least possibly related to ripretinib in 3 of the 4 cases, while noting the majority of patients had at least one risk factor for coronary artery disease. In two of the cases, the reviewer assessed the event as at least possibly related to ripretinib due to insufficient evidence to assess the event as unrelated.

A definitive causal relationship cannot be concluded between cardiac ischemic events and ripretinib; however, given the seriousness of the events, this potential risk should be included in the label. In the absence of any cases occurring on Study DCC-2618-03-001 and the confounding factors in the cases that occurred on Study DCC-2618-01-001, this information is most appropriately located in Clinical Trials Experience (Section 6) and not Warnings and Precautions (Section 5).

Narrative Summaries for Patients with Adverse Event of Cardiac Ischemic Events

DCC-2618-01-001	
SubjectID: (b) (6) **PT:** Acute myocardial infarction **Grade:** 3 **Study Day**: **Dosage:** 200 mg QD (decreased from starting dose) **Reviewer Assessment:** Unrelated.	The patient is a 56 year old female with a diagnosis of Stage IV GIST and medical history significant for coronary artery disease, diabetes mellitus, carotid artery stenosis, hypertension, and tachycardia. On Study Day 64, the patient presented with 1 month history of worsening leg swelling with weight gain of 6 pounds, chest pain with exertion and at night. Laboratory assessments showed elevated troponin level and NT-proBNP. The patient was diagnosed with acute MI. ECHO showed coronary artery disease. Two stents were placed. Day 75 the vent was considered resolved with sequelae. On Day 94, the LVEF was 65%. The drug was restarted. The Applicant assessed the event as unrelated to study drug. The reviewer agrees given the patient's history of coronary artery disease.
SubjectID: (b) (6) **PT:** Cardiac arrest, **Grade**: 5 **Study Day**: 480 **Dosage:** 150 mg BID **Reviewer Assessment:** Possibly related	The patient is a 60 year old female with a diagnosis of Stave IV GIST and medical history significant for ongoing tachycardia. The patient initiated treatment at 150 mg QD. On Study Day 286, the patient's dosage was increased to 150 mg BID. On day 455, the patient discontinued study drug due to progressive disease. On Day 480, 27 days after receiving the last dose of study drug, the patient experienced a cardiac arrest outside of the hospital. Efforts to resuscitate the patient by emergency personnel were unsuccessful. Both the Investigator and the Applicant assessed the death due to cardiac arrest as unrelated to study treatment. This reviewer finds inadequate information to assess whether the fatal event of cardiac arrest is unrelated to ripretinib.
SubjectID: (b) (6) **PT:** Acute coronary syndrome (x 2) **Grade:** 2 **Study Day**: 97 and 541 **Dosage:** 150 mg QD, 50 mg QD **Reviewer Assessment:** Possibly related	The patient is a 48 year old woman with a diagnosis of Stage IV GIST with medical history significant for ongoing coronary artery disease and hypertension. The narrative for this patient noted non-cardiac pain, not acute coronary syndrome as is in the ADAE datafile. The events of acute coronary syndrome were both grade 2 and considered not related by the Investigator. There is insufficient information for the reviewer to assess the nature of the acute coronary syndrome or relatedness to ripretinib.

SubjectID: (b) (6) **PT:** Myocardial infarction **Grade:** 5 **Study Day**: 213 **Dosage:** 150 mg QD **Reviewer Assessment:** Possibly related	The patient is a 73 year old male with a diagnosis of Stage III GIST with medical history significant for ongoing hypertension, chronic kidney disease, and 53-year smoking history. On day 169, echocardiogram showed LVEF of 62% with no wall abnormalities and normal right ventricular size and normal systolic function. On Study Day 195, an ECG showed NSR with evidence of left ventricular hypertrophy without ischemic changes. On Day 213, the patient experienced the SAE of myocardial infarction which ultimately resulted in the patient's death. The Investigator and Applicant assessed the adverse event of fatal myocardial infarction as possible related to the study drug. The reviewer concurs.

- Prolonged QT intervals and Torsade de Pointes
  Analysis using the broad SMQ Torsade de pointes/QT prolongation identified a single case in the ripretinib arm. There were no cases in the placebo arm. The frequency of cardiac arrythmias using the narrow SMQ cardiac arrythmias was similar between the arms with 7% in the ripretinib arm compared to 5% in the placebo arm.

- Hypertension
  The frequency of the grouped term hypertension comprised of the PT hypertension and blood pressure increase was higher in the ripretinib arm (14% Any Grade, 7% Grade 3) compared to in the placebo arm (4.7% Any Grade, 0 Grade 3). The frequency in the ISS was 17%. No additional cases were identified using the Broad SMQ hypertension.

  Compared to the reported vital signs (See 8.2.4), AE reporting underestimates hypertension in both arm while disproportionally reporting more in the ripretinib arm. Based on reported vital signs, 45% of patients in the ripretinib arm and 50% in the placebo arm had at least 1 grade increase. Considering only Grade 3 hypertension, regardless of baseline, 13% of patients in the ripretinib arm had at least one recording of Grade 3 versus 9% of patients in the placebo arm.

  No patients with a reported event of hypertension interrupted, reduced, or discontinued study drug due to the event; therefore, it is unlikely that the cases of hypertension represent symptomatic hypertension. The higher frequency of hypertension in the ripretinib arm based on PT reporting may reflect clinical observation of sustained hypertension as opposed to single vital sign measurements. The allowance of patients with underlying hypertension in Study DCC-2618-03-001 confounds the assessment of causality. However, based upon the higher incidence of hypertension reported in the adverse event dataset (including Grade 3 events) and a mechanistic rationale (i.e., inhibition of VEGFR2), FDA concluded that informing prescribers of this serious risk is warranted in the Warnings and Precautions section of the US Prescribing Information.

- Diarrhea
  The frequency of diarrhea based on the HLT "Diarrhea excl infective" was higher in the ripretinib arm (28%) compared to the placebo arm (14%). The frequency in the ISS was 27%, similar to that observed in the ripretinib arm.

- Arthralgia
  The frequency of the PT arthralgia was higher in the ripretinib arm (18%) compared to the placebo arm (4.7%). The frequency in the ISS was 18%. No additional cases were identified using the HLT Joint related signs and symptoms.

- Myalgia
  The frequency of the PT myalgia was higher in the ripretinib arm (32%) compared to the placebo arm (12%).The frequency in the ISS (36%) was similar to that observed in the ripretinib arm. No additional cases were identified using the HLT muscle pains. Although the frequency of the adverse event muscle pains was high, there were no reports of rhabdomyolysis, and the incidence of Grade ≥ 3 increased creatine kinase, based on laboratory data, was only 1.2% in the ripretinib arm.

- Dermatologic Toxicities
  - PPES: The frequency of the PT palmar-plantar erythrodysesthesia syndrome in the ripretinib arm (21%) was higher compared to the placebo arm (0). The frequency in the ISS was 29%.

  - Alopecia: The frequency of alopecia at the HLT level (52%) was higher in the ripretinib arm compared to the placebo arm (4.7%). The incidence in the ISS (50%) was consistent with the ripretinib arm.

  - Squamous cell carcinoma of the skin was an AECI. As noted in Section 8.2.3 : FDA's Assessment, coding discrepancies were identified for reported cases of squamous cell carcinoma of the skin. Using FDA's hand coding of these adverse events, the frequency of the grouped term squamous cell carcinoma of the skin (SCCS) (comprising the PT squamous cell carcinoma, squamous cell carcinoma of the head and neck, squamous cell carcinoma of the skin, and keratoacanthoma) in the ripretinib arm (4.7%) was higher compared to the placebo arm (0). Similar analysis of the ISS revealed a frequency of 9%.

    Considering other malignancies of the skin, review of adverse events identified 2 cases of melanoma in situ, both occurring in patients in the ripretinib arm. No additional malignancies of the skin were identified. Overall, three cases of melanoma (including the two cases of melanoma in-situ) were identified in the ISS.

- Actinic keratosis: The frequency of actinic keratosis at the PT level in the ripretinib arm (6%) was similar to that observed in the placebo arm (2.3%). The frequency in the ISS was 10%.

- Steven Johnson Syndrome (SJS): There were no cases of Stevens Johnson Syndrome, Erythema Multiforme (EM), or toxic epidermal necrolysis syndrome (TEN) reported in the ripretinib arm or the placebo arm of Study DCC-2618-03-001. One case of SJS and one case of Grade 2 EM was reported in Study DCC-2618-01-001.

  The case of SJS occurred in a 38 year old woman with a diagnosis of GIST who initiated ripretinib at a dosage of 150 mg once daily. On study day 10, the patient experienced peeling feel, hands, and trunk. The patient was treated with oral diphenhydramine, oral acetaminophen, and topical steroid cream. On day 13, oral prednisone with a taper was initiated. On Day 26, the patient was re-challenged at a dosage of 100 mg once daily. Within 2-3 hours, the patient developed signs and symptoms of an allergic reaction (generalized itching, chest tightness, and emesis) but no bullous skin changes. The study drug was discontinued. Of note, this patient was reported to have had a similar reaction to regorafenib. The protocol was subsequently amended to exclude patient with a history of SJS syndrome on a prior tyrosine kinase inhibitor.

  In a response to FDA labeling review comment and information request, the Applicant provided additional information regarding this adverse event. The Applicant noted that the patient, who was never hospitalized and did not have a biopsy, did not have symptoms consistent with the SJS, a severe systemic inflammatory disease characterized by fever, epidermal detachment, skin necrosis, and often conjunctival involvement. At the request of the Applicant, an independent onco-dermatological consultant reviewed the case and concluded per the Applicant that the event did not appear to be SJS and was more likely a hypersensitivity reaction developed from prior tyrosine inhibitor use. The Applicant concluded a diagnosis of SJS is unlikely.

  The aforementioned response to FDA labeling review comment and information request also included additional information regarding the single retrieved case of EM. The Applicant noted that the patient initiated ripretinib at a dosage of 100 mg twice daily. On day 26, Grade 2 EM was reported. The event was not serious, and the patient continued ripretinib at the same dose without interruption. The patient discontinued ripretinib two days after the event due to progressive disease. The Applicant concluded this case is not “representative of a clinical presentation of a bullous, blistering and exfoliative disorder…”

FDA reviewer agrees with the Applicant's assessment that the event reported as SJS is unlikely to represent a true case of SJS. FDA agrees with the Applicant's assessment that the single case of EM does not represent a serious bullous or exfoliative dermatologic event.

In the absence of any cases of SJS or TEN and only a single case of what was reported as Grade 2 EM but that did necessitate interruption of study drug, FDA concludes there is not sufficient evidence to warrant the addition of SJS or other bullous/exfoliative dermatologic toxicities to the label.

- Hyperbilirubinemia
  The frequency of the grouped term hyperbilirubinemia (comprising the PTs blood bilirubinemia increased, blood bilirubinemia, and jaundice) in the ripretinib arm (16%) was higher compared to the placebo arm (2.3%). The frequency in the ISS (18%) was similar to ripretinib arm. Similar results were obtained using the SMQ broad biliary disorders – biliary system related investigations, signs and symptoms. This is consistent to what was observed in the reported laboratory assessments.

Based on the overall assessment of ripretinib as well as the safety profile of similar drugs, FDA evaluated the following additional potential toxicities.

- Hyperlipidemia
  Given the disproportionate incidence of the PT Lipase Increased in the ripretinib arm (11 % Any Grade, 4.7% Grade 3/ 4) compared to the placebo arm (0 Any Grade), FDA performed further assessment on the risk of hyperlipidemia and pancreatitis. There were no cases of pancreatitis reported for either arm.

  Based on laboratory assessments, in the patients who had a baseline assessment and at least one post baseline assessment of lipase, the incidence of elevated lipase in the ripretinib arm was 32% compared to 15 % in the placebo arm. The incidence of Grade 3 was the same in both arms (8%). There were no Grade 4 elevate lipase reported in either arm.

  Review of the laboratory data indicates that adverse event reporting does not accurately reflect laboratory assessments. Based on laboratory data, ripretinib appears associated with a risk of Grade 1 or 2 increased lipase; however, it does not appear associated with an increased risk of Grade ≥3 increased lipase.

- Liver toxicity (not including hyperbilirubinemia).
  - Liver failure: There were no cases of liver failure reported in the ripretinib arm, placebo arm, or the ISS.
  - Transaminitis: The frequency of abnormal liver transaminases based on the PT AST increased and PT ALT increased was similar in the ripretinib arm (7%) compared to

the placebo arm (4.7) and the ISS (9%). This is consistent to what was observed in the reported laboratory assessments.

- Renal Toxicity
  Two patients had the TEAE of renal failure during double blinded period on DCC-2618-03-001 (0 in the ripretinib arm and 2 in the placebo arm). Three patients had the PT of renal failure in the ISS (0.8), all were Grade 1 or 2.

  The frequency of the grouped term renal injury (comprising the PTs acute kidney injury, azotemia, chronic kidney disease, renal failure, and blood creatinine increased) was 9% in the ripretinib arm, the placebo arm, and the ISS.

  Based on the laboratory assessment of creatinine, the rate of increased creatinine (Grades 1 and 2) was lower in the ripretinib arm compared to the placebo arm. There were no grade 3 or grade 4 increases in creatinine in either arm.

- Hemorrhage
  The frequency of the grouped term hemorrhage (comprising the PTs anal hemorrhage, brain stem hemorrhage, cerebral hemorrhage, gastric hemorrhage, gastrointestinal hemorrhage, hemorrhage, hemorrhage intracranial, hemorrhagic anemia, hemorrhoidal hemorrhage, hepatic hemorrhage, internal hemorrhage, intra-abdominal hemorrhage, lower gastrointestinal hemorrhage, mouth hemorrhage, periorbital hemorrhage, peritoneal hemorrhage, rectal hemorrhage, tumor hemorrhage, upper gastrointestinal hemorrhage, uterine hemorrhage, and vaginal hemorrhage) was 3/85 (3.5%) in patients in the ripretinib arm, with 1 patient having gastrointestinal hemorrhage (grade 1), 1 patient having upper gastrointestinal hemorrhage (grade 3), and 1 patient having vaginal hemorrhage (grade 1). No patient had an event from the grouped term hemorrhage. The frequency was 10% (36/351) in the ISS. The relatively high frequency in the ISS is not mirrored in the ripretinib arm on the randomized control trial during the blinded period and likely reflects a population with more advanced disease.

  Review of narratives for patients with serious adverse events of hemorrhage did not provide compelling evidence suggesting the use of ripretinib is associated with increased risk of serious hemorrhage.

- Thromboembolic Events
  The frequency of the HLGT embolism and thrombosis was similar in the ripretinib arm (1.2%), the placebo arm (2.3%), and the ISS (4%).

- Cytopenias
  The frequency of the grouped term cytopenias (comprising the PTs anemia, anemia of chronic disease, anemia of malignant disease, normocytic anemia, neutropenia, thrombocytopenia, lymphocyte count decreased, platelet count decreased, and white blood cell count decreased) was similar in the ripretinib arm (15%) compared to the placebo arm (19%). The frequency in the ISS was 25%. Based on laboratory assessments, the frequency of decreased neutrophils was greater in the ripretinib arm (11%) compared to the placebo arm (2.5), and the frequency of decreased platelets was higher in the ripretinib arm (8%) compared to the placebo arm (0). For both parameters there were no Grade 4 events in either arm.

- Edema
  The frequency of the grouped term edema (comprising the PTs generalized edema and edema peripheral) was slightly higher in the ripretinib arm (16%) compared to the placebo arm (9%). The frequency was 12% in the ISS.

Adverse Reactions:

Adverse reactions are adverse events considered to be causally related to a drug. In the setting of a randomized placebo controlled trial, they may be identified as those that occur with significantly greater frequency in the treatment arm than in the placebo arm. The table below shows the adverse reactions, defined as adverse events occurring at least 10% more frequently in the ripretinib arm than in the placebo arm. The majority of these adverse reactions were Grade 1 and 2.

Table 22.2. Adverse Reactions Occurring More Frequently in Ripretinib Arm (≥ 10%) during Double-Blinded Period in Study DCC-2618-03-001

Preferred Term	Ripretinib (N = 85) all % (Grade3-4 %)	Placebo (N = 43) all % (Grade3-4 %)	Difference
Alopecia	52 (0)	5(0)	+47
Fatigue	42 (3.5)	23 (2.3)	+19
Nausea	39 (3.5)	12 (0)	+27
Constipation	34 (1.2)	19 (0)	+16
Myalgia	32 (1.2)	12 (0)	+20
Diarrhea	28 (1.2)	14 (2.3)	+14
PPES	21(0)	0	+21
Vomiting	21 (3.5)	7 (0)	+14
Headache	19 (0)	5 (0)	+14
Arthralgia	18 (0)	5 (0)	+13

Blood bilirubin increased	16 (1.2)	0	+16
Muscle spasms	15 (0)	5 (0)	+11
Dyspnea	13 (0)	0	+13
Hypophosphatemia	11 (4.7)	0	+11
Lipase increased	11 (4.7)	0	+11
Stomatitis	11 (0)	0	+11

Source: Reviewer table based on ADAE dataset

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:

Not applicable

The Regulatory Authorities' Assessment:

The Regulatory Authorities agree with the Applicant's assessment.

8.2.7. Safety Analyses by Demographic Subgroups

The Applicant's Position:
Subgroup analyses of TEAEs and SAEs by age, gender, race, geographic region, and BMI were conducted. Overall, results observed for subgroup analyses were similar to the safety results observed in the analysis pools and results for patients in the ≥ 4th line of treatment group.

The Regulatory Authorities' Assessment:

TEAS by Gender

The table below summarizes AEs for the ripretinib arm of DCC-2618-03-001 and the ISS by gender. In the ripretinib arm, female patients appear to have slightly higher frequency of Grade 3-4 TEAEs and TEAEs leading to discontinuation. This was not recapitulated to the same extent in the ISS. Analysis comparing the frequency of individual TEAEs by age in the ripretinib arm identified the following differences: the following TEAEs were observed more frequently in females than males (≥ 20% difference): alopecia (66% v. 40%), PPES (34% v. 11%), myalgia (45% v. 21%), and nausea 50% v. 30%). The following TEAE was observed less frequently in females

than males (≥20% difference): anemia (2.6% v. 23%).

Some differences are to be expected due to chance alone, and given the limited number of patients in each group, a true interaction between gender and these differences cannot be concluded. Thus, no gender specific labeling is indicated.

Table 22.3. Overall Summary of Adverse Events by Gender in Study DCC-2618-03-001 Ripretinib Arm and Integrated Safety Set (ISS)

	Ripretinib Arm		ISS	
	Female N=38 n (%)	Male N=47 n (%)	Female N=141 n (%)	Male N=210 n (%)
Any TEAE	38 (100)	46 (98)	141 (100)	209 (100)
Grade 3-4 TEAE	21 (55)	21 (45)	96 (68)	126 (60)
Serious Adverse Event	11(29)	15 (32)	67 (48)	103 (49)
TEAE leading to discontinuation	5(13)	2 (4.2)	20 (14)	22 (10)
TEAE leading to interruption	9(24)	11 (23)	58 (41)	91 (43)
TEAE leading to reduction	3(8)	3 (6)	11 (8)	6 (2.9)
Multiple Actions Taken (primarily interrupted and reduced)	NA	NA	16 (11)	14 (7)

Source: Reviewer table based on DCC-2618-03-001: ADAE and ISS: ADAE datasets.

TEAS by Age

The table below summarizes AEs for the ripretinib arm of DCC-2618-03-001 and the ISS by age. Patients were categorized as < 65 years or age of ≥ 65 years of age. This was similarly observed in the ISS. In the ripretinib arm, older patients appear to have slightly higher frequency of serious adverse events and adverse events leading to discontinuation. Analysis comparing the frequency of individual AEs between age groups did not identify any differences ≥ 20%.

Some differences are to be expected due to chance alone and given the limited number of patients in each group, a true interaction between age and these differences could not be concluded. Thus, no age specific labeling is indicated.

Table 22.4. Overall Summary of Adverse Events by Age Group in DCC-2618-03-001 Ripretinib Arm and Integrated Safety Set

	Ripretinib Arm		ISS*	
	< 65 years N=57 n (%)	≥ 65 years N=28 n (%)	< 65 years N=221 n (%)	≥ 65 years N= 130 n (%)
Any TEAE	57 (100)	27 (96)	220 (100)	130 (100)
Grade 3-4 TEAE	28 (49)	14 (50)	132 (60)	90 (69)
Serious Adverse Event	15 (26)	11 (39)	100 (45)	70 (54)
TEAE leading to discontinuation	2 (3.5)	5 (18)	25 (11)	17 (13)
TEAE leading to interruption	14 (25)	6 (21)	80 (36)	69 (53)
TEAE leading to reduction	5 (9)	1 (3.6)	12 (5)	5 (3.8)
Multiple Actions Taken (primarily interrupted and reduced)	NA	NA	15 (7)	15 (12)

Source: Reviewer table based on DCC-2618-03-001: ADAE and ISS: ADAE datasets.

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:
Not applicable.

The FDA's Assessment:

Not applicable.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development
The Applicant's Position:

Carcinogenicity studies have not been conducted with ripretinib.

The Regulatory Authorities' Assessment:

The Regulatory Authorities agree with the Applicant's assessment.

Human Reproduction and Pregnancy
The Applicant's Position:

There are no clinical data on the use of ripretinib in pregnant women. There were no reported pregnancies or lactation events reported in the ripretinib clinical development program.

Females of reproductive potential and males with female partners of reproductive potential should use effective contraception during treatment and for at least 4 months after the last dose of ripretinib.

The Regulatory Authorities' Assessment:

The Regulatory Authorities agree with the Applicant's assessment.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

Gastrointestinal stromal tumors are very rare in children and adolescents. GIST patients under 21 years of age constitute only 2.7% of gastric and 0.6% of intestinal GIST cases [Miettinen, 2005; Miettinen, 2006]. The United Kingdom National Registry of Childhood Tumors reported an annual incidence of 0.02 per million for children under the age of 14 [Benesch, 2009]. In addition to this, ripretinib was granted orphan drug designation (ODD# 14-4474) by FDA for treatment of GIST on October 2, 2014. In accordance with 21 CFR 314.55(5)(d), orphan drugs are exempt from the pediatric study requirements in 21 CFR 314.55.

The Regulatory Authorities' Assessment:

The Applicant did not submit any data regarding safety in pediatric population.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

Based on the mechanism of action, withdrawal or rebound effects are not anticipated with ripretinib; drug abuse is not anticipated with ripretinib. There have been no cases of treatment overdose in Phase 1 and Phase 3 studies

The Regulatory Authorities' Assessment:

The Regulatory Authorities agree with Applicant's assessment.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:
Not applicable; ripretinib has not yet been marketed in any country.

The Regulatory Authorities' Assessment:

The Regulatory Authorities acknowledge the Applicant's position that ripretinib has not received marketing approval in any country.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:
Potential safety concerns beyond the risks observed in clinical trials and conveyed in the proposed labeling are not expected. Routine pharmacovigilance will be conducted to monitor for unexpected adverse events.

The Regulatory Authorities' Assessment:

The Regulatory Authorities agree.

8.2.11. Integrated Assessment of Safety

The Applicant's Position:

The overall safety profile of ripretinib is acceptable relative to the benefits in the context of the treatment of this life-threatening disease. Based on the evaluation of the safety data in patients who received ripretinib at the recommended dose of 150 mg QD, ripretinib has an acceptable safety profile in patients with advanced GIST who have received 3 prior therapies and have no other available treatment options.

Overall safety was well characterized in the intended target population. In Study DCC-2618-03-001, relatively similar proportions of patients reported AEs (98.8% vs 97.7%), grade 3/4 AEs (49.4% vs. 44.2%), SAEs (30.6% vs. 44.2%), AEs leading to treatment discontinuation (8.2% vs. 11.6%), AEs leading to dose reduction (7.1% vs. 2.3%), AEs leading to dose interruption (23.5% vs. 20.9%) in the ripretinib group than in the placebo group, respectively.

Adverse events of clinical interest, which were also considered to be risks associated with ripretinib treatment include; important identified risks hand-foot skin reaction (HFSR) [PPES], and hypertension. Important potential risk includes squamous cell carcinoma (SCC) of skin. These events were managed by appropriate supportive medical care and/or dose modifications. Identified risks include alopecia, myalgia, arthralgia, diarrhea, and cardiac failure. Potential risks include hyperbilirubinemia and Stevens-Johnson syndrome.

Important identified or potential risks with ripretinib and recommendation for treatment and mitigation are summarized below.

Dermatologic Toxicities
Dermatologic risks are described below.

Hand-Foot Skin Reaction (Palmar-Plantar Erythrodysesthesia Syndrome)
Palmar-plantar erythrodysesthesia syndrome was reported in 18 of 85 (21.1%) patients in the ripretinib arm and no patients in the placebo arm during the double-blind period of Study DCC-2618-03-001. All events were mild or moderate in severity. It is recommended to consider topical treatment if a patient develops such an event. Dose interruption or reduction may be appropriate.

Squamous Cell Carcinoma of the Skin
SCC of the skin occurred in 2 of 85 (2.4%) patients in the ripretinib arm and no patients in the placebo arm during the double-blind period of Study DCC-2618-03-001. No action was taken with ripretinib, and both events resolved. Routine dermatologic examinations are recommended for patients taking ripretinib.

Hypertension
Hypertension occurred in 12 of 85 (14.1%) of patients in the ripretinib arm and 2 of 43 (4.7%) patients in the placebo arm during the double-blind period of Study DCC-2618-03-001. Hypertension was severe (grade 3) in 6 (7.1%) patients in the ripretinib arm. It is recommended that patients have adequately controlled blood pressure prior to initiating treatment with ripretinib and that blood pressure be regularly monitored during treatment with ripretinib. If severe or uncontrolled hypertension occurs, it is recommended to hold, reduce, or discontinue ripretinib.

Wound Healing
Per protocol, patients were asked to interrupt use of ripretinib prior to surgery. Though no formal study of the effect of ripretinib on wound healing has been performed, temporary interruption of ripretinib is recommended for precautionary reasons in patients undergoing major surgical procedures.

The Regulatory Authorities' Assessment:

The evaluation of the safety of ripretinib 150 mg once daily in patients with advanced GIST who have received prior treatment with imatinib, sunitinib, and regorafenib was based primarily on 128 patients randomized in the DCC-2618-03-001 trial who received at least one dose of study drug (ripretinib: 85 patients, placebo: 43 patients). The review also included analysis of a pooled dataset of 295 patients with advanced malignancies with a molecular rationale for

activity, who received at least one dose of ripretinib 150 mg once daily. Analysis of the pooled dataset validated the results of the analyses of DCC-2618-03-001 and did not identify any new serious but rare safety signal.

Study DCC-2618-03-001 excluded patients who were at increased risk for toxicities observed in other studies with ripretinib as well as the known toxicities of similar kinase inhibitors. Such exclusion criteria included the following:

- Significant heart disease (NYA class II-IV), active ischemia, or any other uncontrolled cardiac condition including arrhythmias, uncontrolled hypertension, or cardiac heart failure.
- History of arterial thrombotic or embolic events within 6 months of planned study treatment initiation.
- QTc > 450 ms in males or > 470 in females or history of long QTc.

In Study DCC-2618-03-001, the median exposure was 23.9 weeks (range 1.3 weeks to 59.4) in the ripretinib arm versus 6 weeks (range 0.4 to 38.4) in the placebo arm; 46% of patients received ripretinib for at least 6 months.

The table below summarizes the overall safety profile of ripretinib 150 mg QD as observed on DCC-2618-03-001. Overall, ripretinib was well tolerated with the frequency of adverse events (all grades, Grade 3-4, and serious) similar between the arms. The frequency of treatment discontinuations, interruptions, and reductions was also comparable between arms.

Table 22.5. Summary of Treatment Emergent Events During Blinded Period in Study DCC-2618-03-001

	Ripretinib N=85 n (%)	Placebo N=43 n %
All-Grade AEs	84 (99)	42 (98)
Grade 3-4 AEs	42 (49)	19 (44)
Serious AEs	26 (31)	19 (44)
Fatal AEs *	5 (6)	10 (23)
Treatment D/C due to AEs	7 (8)	5 (12)
Dose interruption due to AE	20 (24)	9 (21)
Dose reduction due to AE	6 (7)	1 (2.3)

* Includes deaths due to disease progression.
Source: Reviewer table based on DCC-2618-03-001: ADAE dataset

Adverse reactions associated with ripretinib were primarily gastrointestinal disorders, dermatologic conditions, and musculoskeletal and connective tissue disorders. The most common adverse drug reactions (not including laboratory abnormalities) observed in the ripretinib arm occurring in at least 10% of patients and with a frequency at least 10% greater than in the placebo arm were: alopecia (52%), nausea (39%), fatigue (42%), constipation (34), myalgia (32%), diarrhea (28%), PPES (21%), vomiting (21%), arthralgia (18%), headache (18%), muscle spasms (15%), dyspnea (13%), and stomatitis (11). The majority of these adverse reactions were Grade 1-2 in severity.

The incidence of laboratory abnormalities for which the incidence of Grade 1-3 abnormalities was at least 5 % higher in the ripretinib arm compared to the placebo arm were: decreased neutrophils, decreased platelets, decreased white blood cells, increased lipase, decreased phosphorous, decreased calcium, increased creatine kinase, increased bilirubin, decreased sodium, increased amylase, decreased potassium, increased magnesium, and increased APTT. Only for decreased phosphorous was the incidence of Grade 3 abnormalities at least 5% different in the ripretinib arm.

Other less common but serious adverse reactions observed with increased frequency in the ripretinib arm include hypertension, squamous cell carcinoma of the skin, and cardiac dysfunction.

The following serious adverse reactions observed with other kinase inhibitors were not observed in the ripretinib arm or were reported with frequencies similar to that observed in the placebo arm: prolonged QTc/ Torsade's de Pointe, liver failure and transaminitis, renal toxicity including renal injury and increased creatinine, edema, and thromboembolic events.

The safety profile of ripretinib 150 mg once daily in patients with advanced GIST who have received prior treatment with imatinib, sunitinib, and regorafenib is acceptable with most adverse reactions being Grade 1 or 2 and higher grade toxicities adequately managed through temporary interruption or dose reduction.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

No major statistical issues were identified while reviewing the data and results submitted in this application; however, FDA noted an imbalance between the treatment groups with respect to older patients. Additional analyses were performed to assess the impact of this imbalance on the primary and key secondary endpoints considered in the study. In general, the results appear to be robust and there was no impact on the conclusions.

8.4. Conclusions and Recommendations

The FDA's Assessment:

The FDA agrees that the results of Study DCC-2618-03-001 (INVICTUS) demonstrate that ripretinib provides a statistically significant and clinically meaningful improvement in progression free survival in patients who were randomized to receive ripretinib compared to patients randomized to receive placebo. Progression-free survival is considered by FDA to be an acceptable endpoint to demonstrate the effectiveness of new therapeutics across many oncology indications and has been the primary basis for approval of therapies indicated for the treatment of advanced GIST. Study DCC-2618-03-001 provides the evidence that supports the effectiveness of ripretinib in patients with GIST who have previously received imatinib, sunitinib, and regorafenib. The safety profile of ripretinib 150 mg once daily is acceptable in the context of patients with a serious and life-threatening condition and limited treatment options, and is manageable with guidelines provided in product labeling, Overall, the review team deems the benefit:risk assessment of ripretinib in the indicated population to be favorable and recommends regular approval for the following indication:

QINLOCK is a kinase inhibitor indicated for the treatment of adult patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with 3 or more kinase inhibitors, including imatinib.

X	X
Primary Statistical Reviewer Sirisha Mushti, Ph.D.	Statistical Team Leader Lisa Rodriguez, Ph.D.
X	X
Primary Clinical Reviewers Leslie Doros, M.D. (Efficacy) Margaret Thompson, M.D. (Safety)	Clinical Team Leader Lola Fashoyin-Aje, M.D., M.P.H.

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

No major review issues were identified during the review of this application and thus, the review team did not seek input from external consultants or refer the application to the Oncologic Drug Advisory Committee.

10 Pediatrics

The Applicant's Position:

N/A

The FDA's Assessment:

Ripretinib was granted orphan drug designation for treatment of GIST and in accordance with 21 CFR 314.55(5)(d), orphan drugs are exempt from the pediatric study requirements in 21 CFR 314.55.

11 Labeling Recommendations

The Applicant's Position:

The final draft United States Prescribing Information (USPI) for QINLOCK (ripretinib) was submitted with the NDA on November 19, 2019.

The FDA's Assessment:

The table below summarizes changes to the proposed prescribing information (PI) made by FDA. See the final approved prescribing information for QINLOCK (ripretinib) accompanying the approval letter for more information.

Highlights of Significant Labeling Changes (High-Level Changes)

Section	Proposed Labeling	Approved Labeling
Full Prescribing Information		
Indications and Usage	(b) (4)	Amended to patients who have received prior treatment with 3 or more kinase inhibitors, including imatinib.
Dosage and Administration Dosage Modifications for Adverse Reactions		(b) (4) Added left ventricular systolic dysfunction to Table (b) (4)
Warnings and Precautions		Divided Dermatologic Toxicities into

	(b) (4)	two separate W&Ps: Palmar-Plantar Erythrodysesthesia Syndrome (5.1) and a new W&P for New Primary Cutaneous Malignancies (5.2), which includes information pertaining to cutaneous squamous cell carcinoma and melanoma. Added new W&P for cardiac dysfunction, based on totality of evidence in which this rare but serious event cannot be ruled out as related to QINLOCK. (b) (4) Modified the W&P for Wound Healing to provide specific recommendations for when to withhold and resume QINLOCK for surgery. The recommendations are consistent with labeling for other drug products that inhibit VEGF signaling.
Adverse Reactions	AR listed by decreasing order.	Added data to describe the pooled safety population in the W&P. Modified AR table to be grouped by body system in decreasing order.
	(b) (4)	
	(b) (4)	Revised the Grades 1-4 column of the laboratory table (b) (4) (b) (4) (b) (4) and in the Grades 3-4 column, (b) (4) Modified laboratory table to group by category with order based on the AR with the highest incidence within a given category. Added "Other Adverse Reactions" to

		capture clinically relevant ARs occurring in < 10% of patients and included cardiac ischemic events in this list.
Drug Interactions	Included one table for strong (b) (4) (b) (4) CYP3A inhibitors.	Added a table for strong CYP3A inducers to provide information for potential interactions (b) (4) (b) (4)
Specific Populations Pregnancy	Included data in pregnant rats.	Added data in rabbits to highlight pregnancy loss.
Specific Populations Lactation	(b) (4)	Modified to avoid breast-feeding during treatment and for 1 week after the final dose based on the elimination half-life.
Specific Populations Females and Males of Reproductive Potential		Modified to use contraception during treatment and for 1 week after final dose based on elimination half-life based on recommendations found in Oncology Pharmaceuticals: Reproductive Toxicity Testing guidance.
Specific Populations Pediatric Use		Added animal toxicology data.
Specific Populations Geriatric Use	(b) (4)	Revised to state that there were too few patients 65 and older to make a conclusion.
(b) (4)		
Clinical Pharmacology Pharmacokinetics	(b) (4)	Modified to include PK parameters for the active metabolite, DP-5439. (b) (4) included this information in the general statement under the heading Use in Specific Populations in the absence of a specific dose adjustment recommendation or clinically relevant information.

	Drug Interaction Studies	Added language to clarify that the effect of CYP3A4 inducer on ripretinib exposure has not been studied.
Clinical Studies	Included a table describing efficacy results.	Modified table to include number and percentage progressive disease and death.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

The risks of ripretinib are acceptable in the indicated patient population with a serious and life-threatening condition; the safe use of ripretinib can be adequately implemented in the post-marketing setting through product labeling. No additional risk management strategies are recommended.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

The review team recommends issuing the following postmarketing requirement (PMRs) and postmarketing commitments (PMCs)

Clinical pharmacology PMRs:

1. Submit data from the hepatic impairment study.

2. Submit data evaluating the effect of co-administration of ripretinib with CYP2C8 substrates.

Clinical pharmacology PMCs:

1. Submit data evaluating the effect of co-administration of ripretinib with rifampin (strong CYP3A inducer).
2. Submit a PBPK modeling report estimating the effect of co-administration of ripretinib with a moderate CYP3A inducer.

14 Division Director (DHOT) (NME ONLY)

X

15 Division Director (OCP)

X

16 Division Director (OB)

X

17 Division Director (Clinical)

I concur with the clinical review team's assessment of the clinical evidence provided in this application and with the conclusions and, agree with the recommendation to grant the Applicant's request for approval.

X

Lola Fashoyin-Aje, M.D., M.P.H.
Deputy Director (acting), Division of Oncology 3

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X _____

19 Appendices

19.1. References

1. Aubin F and Blanke CD. Metastatic gastrointestinal stromal tumors. *Cancer Chemother Pharmacol.* 2011; 67(Suppl 1): S9-S14. DOI 10.1007/s00280-010-1512-9.

2. Ben-Ami E, Barysauskas CM, von Mehren M, Heinrich MC, Corless CL, Butrynski JE, Morgan JA, Wagner AJ, Choy E, Yap JT, Van den Abbeele AD, Solomon SM, Fletcher JA, Demetri GD, George S. *Ann Oncol*. 2016 Sep; 27(9):1794-9.

3. Benesch M, Wardelmann E, Ferrari A, Brennan B, Verschuur A. Gastrointestinal stromal tumors (GIST) in children and adolescents: A comprehensive review of the current literature. *Pediatric Blood & Cancer*. 2009. 53:1171–1179.

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

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

6. Boikos SA, Pappo AS, Killian JK, LaQuaglia MP, Weldon CB, George S, Trent JC, von Mehren M, Wright JA, Schiffman JD, Raygada M, Pacak K, Meltzer PS, Miettinen MM, Stratakis C, Janeway KA, Helman LJ. Molecular subtypes of KIT/PDGFRA wild-type gastrointestinal stromal tumors: a report from the national institutes of health gastrointestinal stromal tumor clinic. *JAMA Oncol*. 2016;2:922–8.

7. Care RS, Valk PJ, Goodeve AC, Abu-Duhier FM, Geertsma-Kleinekoort WM, Wilson GA, et al. Incidence and prognosis of c-KIT and FLT3 mutations in core binding factor (CBF) acute myeloid leukaemias. *British Journal of Haematology*. 2003;121(5):775-7.

8. Cassier, P, et al. Outcome of Patients with Platelet-Derived Growth Factor Receptor Alpha–Mutated Gastrointestinal Stromal Tumors in the Tyrosine Kinase Inhibitor Era. *Clin Cancer Res*. August 15 2012 (18) (16) 4458-4464; DOI: 10.1158/1078-0432.CCR-11-3025.

9. Casali, et al, Gastrointestinal stromal tumours: ESMO–EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up, *Annals of Oncology*, Volume 29, Issue Supplement_4, October 2018, Pages iv68–iv78, https://doi.org/10.1093/annonc/mdy095.

10. Corless CL, Barnett CM, and Heinrich MC. Gastrointestinal stromal tumours: origin and molecular oncology. Nature Reviews. *Cancer*. 2011;11:865-878.

11. Corless, CL. Gastrointestinal stromal tumors: what do you know now? *Mod Path*. 2014; 27 (S2-S16).

12. Corless CL and Heinrich MC. Molecular pathobiology of gastrointestinal stromal sarcomas. *Annu Rev Pathol*. 2008;3:557-86.

13. Demetri GD, Benjamin RS, Blanke CD, et.al. NCCN Task Force Report: Optimal management of patients with gastrointestinal stromal tumor (GIST) – update of the NCCN clinical practice guidelines. *JNCCN*. 2007;5(2):S1-S32.

14. Demetri GD, Reichardt P, Kang YK, et.al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib: an international, multicenter, prospective, randomized, placebo-controlled phase 3 trial (GRID). *Lancet*. 2013;381(9863): doi:10.1016/S0140-6736(12)61857-1.

15. Eisenberg BL and Smith KD. Adjuvant and neoadjuvant therapy for primary GIST. *Cancer Chemother Pharmacol*. 2011; 67 (Suppl 1):S3–S8. DOI 10.1007/s00280-010-1516-5.

16. Emile JF, Brahimi S, Coindre JM, et.al. Frequencies of KIT and PDGFRA mutations in the MolecGIST prospective population-based study differ from those of advanced GISTs. *Med Oncol*. 2011. DOI 10.1007/s12032-011-0074-y.

17. ESMO. Gastrointestinal stromal tumors: ESMO-EURACAN clinical practice guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2018;29(Suppl 4): iv68–iv78. doi: 10.1093/annonc/mdy095.

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

19. George S, Wang Q, Heinrich MC, et.al. Efficacy and safety of regorafenib in patients with metastatic and/or unresectable GI stromal tumor after failure of imatinib and sunitinib: a multicenter phase II trial. *J Clin Oncol*. 2012;30(19):2401-2407.

20. GLEEVEC® US Package Insert 2019.

21. Heinrich MC, Corless CL, Duensing A, et al. PDGFRA activating mutations in gastrointestinal stromal tumors. *Science*. 2003;299(5607):708-710.

22. Heinrich MC, Maki RG, Corless CL, et al. Primary and secondary kinase genotypes correlate with the biological and clinical activity of sunitinib in imatinib-resistant gastrointestinal stromal tumor. *J Clin Oncol* . 2008;26:5352-9. 10.1200/JCO.2007.15.7461.

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

24. Kee D, and Zalcberg JR. Current and emerging strategies for the management of imatinib-refractory advanced gastrointestinal stromal tumors. *Ther Adv Med Oncol*. 2012;4(5):255-270.

25. Maleddu A, Pantaleo MA, Nannini M, and Biasco G. The role of mutational analysis of KIT and PDGFRA in gastrointestinal stromal tumors in a clinical setting. *Journal of Translational Medicine*. 2011;9:75. doi:10.1186/1479-5876-9-75.

26. Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. *Am J Surg Pathol*. 2005 Jan;29(1):52-68.

27. Miettinen M, Makhlouf H, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the jejunum and ileum: a clinicopathologic, immunohistochemical, and molecular genetic study of 906 cases before imatinib with long-term follow-up. *Am J Surg Pathol*. 2006 Apr;30(4):477-89.

28. Nannini M, Biasco G, Astolfi A, Pantaleo MA. An overview on molecular biology of KIT/PDGFRA wild-type (WT) gastrointestinal stromal tumours (GIST). *J Med Genet*. 2013;50:653–61.

29. Pantaleo MA, Nannini M, Corless CL, Heinrich MC. Quadruple wild-type (WT) GIST: defining the subset of GISTs that lack abnormalities of KIT, PDGFRA, SDH, and the RAS signalling pathway. *Cancer Med*. 2015;4:101–3.

30. Rubin BP, Singer S, Tsao C, et.al. KIT activation is a ubiquitous feature of gastrointestinal stromal tumors. *Cancer Research*. 2001; 61:8118-8121.

31. Søreide K, Oddvar MS, Søreide JA, Giljaca V, Jureckova A Bulusue VR. Global epidemiology of gastrointestinal stromal tumours (GIST): A systematic review of population-based cohort

studies; *Cancer Epidemiology.* 2016; 40:39-46.

32. STIVARGA® US Package Insert 2019.

33. SUTENT® (sunitinib malate) capsules US Package Insert. Pfizer Labs. Revised 5/2019.

34. Tran T, Davila JA, and El-Serag HB. The epidemiology of malignant gastrointestinal stromal tumors: an analysis of 1,458 cases from 1992 to 2000. *Am J Gastroenterol*. 2005 Jan;100(1):162-8.

35. Yoo C, Ryu MH, Jo J, Park I, Ryoo BY, Kang YK. Efficacy of Imatinib in Patients with Platelet-Derived Growth Factor Receptor Alpha-Mutated Gastrointestinal Stromal Tumors. *Cancer Res Treat*. 2016;48(2):546–552.

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

The FDA's References:

1. Jumniensuk C and Charoenpitakchai. Gastrointestinal Stromal Tumor: Clinicopathological Characteristics and Pathologic Prognostic Analysis. *World J Surg Oncol.* 2018;16:231.

2. SEER (2019) https://www.cancer.org/cancer/gastrointestinal-stromal-tumor/detection-diagnosis-staging/survival-rates.html

3. Subramanian S, West RB, Corless CL, Ou W, et al. Gastrointestinal Stromal Tumots (GIST) with KIT and PDGFRA mutations Have a Distinct Gene Expression Profile. *Oncogene.* 2004;23(47):7780-90.

19.2. Financial Disclosure

The Applicant's Position:

The Applicant provided financial disclosure for all clinical investigators involved in the studies included in this submission in Form 3455. No concerns were raised regarding the overall integrity of the data. There were two principal investigators with disclosable financial arrangements (Table 23).

Table 23: Summary of Disclosable Financial Arrangements and Interest

Investigator	Study No.	Center No	Amount Disclosed	Category of Disclosure
(b) (6)	DCC-2618-01-001	(b) (4)	>$25000	Significant payments of other sorts (SPOOS); research funding
	DCC-2618-03-001 (INVICTUS)		>$25000	Significant payments of other sorts (SPOOS); research funding
	DCC-2618-03-001 (INVICTUS)		>$25000	Significant payments of other sorts (SPOOS); research funding

The FDA's Assessment:

In Study DCC-2618-01-001, there were 354 investigators at sites that enrolled patients and in Study DCC-2618-03-001 there were 257 investigators at sites that enrolled patients. Signed financial disclosure forms could not be obtained for three sub-investigators for Study DCC-2618-01-001. The Applicant acted with due diligence to obtain financial disclosures directly from all three sub-investigators.

Covered Clinical Study (Name and/or Number):*

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 611		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 608		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

19.3. OCP Appendices (Technical documents supporting OCP recommendations)

The FDA's Assessment:

19.3.1 Summary of Bioanalytical Method Validation and Performance

The concentrations of ripretinib and DP-5439 in plasma, urine, and feces were measured in clinical studies using validated liquid chromatography with tandem mass spectrometry/mass spectrometry (LC-MS/MS) methods. Overall, the precision, accuracy, selectivity and performance of the methods used to analyze ripretinib and DP-5439 in plasma were acceptable and within the FDA guidance recommended criteria.

Two bioanalytical methods, VDECI1500P1 (used in clinical Studies DCC-2618-01-001 and DCC-2618-03-001) and V1471901P1 (used in clinical Studies DCC-2618-01-002 and DCC-2618-01-003), were developed and validated for measuring ripretinib and DP-5439 in human plasma by LC-MS/MS. IN both methods, ripretinib and DP-5439, were released from the human plasma by protein precipitation. After protein precipitation, the supernatant was chromatographed using (b) (4) HPLC with a Betasil C8 analytical column. Ripretinib and DP-5439 were detected by monitoring the precursor and product ions (Ripretinib; m/z 510.3 -> 417 and DP-5439; m/z 496.2 -> 403) using an Applied Biosystems Sciex API5000 or API5500 LC-MS/MS. A summary of the validation results of methods VDECI1500P1 and V1471901P1 is provided in Table 24. Ripretinib and DP-5439 in human plasma, with K2EDTA as anticoagulant, was proven to be stable during blood collection processing for up to 1 hour, at room temperature under normal laboratory lighting over a period of 16 hours, at -20 °C or -70 °C over a period of 137 days in polypropylene tubes, over 4 cycles of freeze (-20 °C and -70 °C) and thaw (room temperature), at room temperature stored in glass vials over a period of 2 days 23 hours (autosampler) with and without the presence of itraconazole or pantoprazole.

The bioanalytical method V1471804U2 (used in Study DCC-2618-01-003) was developed and validated for measuring ripretinib and DP-5439 in human urine by LC-MS/MS. Ripretinib and DP-5439, were released from the samples by dilution. After dilution, the samples were chromatographed using (b) (4) HPLC with a Betasil phenyl analytical column. The analytes were detected using an Applied Biosystems Sciex API 5000 LC-MS/MS. The validation results showed that the method V1471804U2 was linear over the range of 1.0 to 800 ng/mL for both ripretinib and DP-5439 and could quantify ripretinib and DP-5439 in human urine with acceptable precision and accuracy. Ripretinib and DP-5439 have been demonstrated to be stable in human urine treated with Tween 20 over 8 cycles of freeze (-20°C and -70°C) and thaw (room temperature), at room temperature under normal laboratory lighting over a period of 97 hours, and after long-term storage at -20°C and -70°C for 170 days.

The bioanalytical method V1471804F1 (used in Study DCC-2618-01-003) was developed and validated for measuring ripretinib and DP-5439 in human fecal homogenate. Ripretinib and DP-5439, were released from samples by protein precipitation. After protein precipitation, the supernatants were chromatographed using (b) (4) HPLC with a Betasil C8 analytical column. The analytes were detected using LC-MS/MS. The validation results showed that this method could quantitatively measure ripretinib and DP-5439 in human fecal homogenate with acceptable precision and accuracy. The linear range was 20.0 to 10000 ng/mL for both ripretinib and DP-5439. Ripretinib and DP-5439 have been demonstrated to be stable in fecal homogenate over 4 cycles of freeze (-20°C and -70°C) and thaw (room temperature), at room temperature under normal laboratory lighting over a period of 24 hours, and in the long term at -20°C and -70°C for 76 days.

Table 24: Summary method performance of a bioanalytical methods VDECI1500P1 and V1471901P1 to measure ripretinib and DP-5439 in human plasma.

Methodology – V1471901P1	**Method Performance – LC-MS/MS**	
	Ripretinib	**DP-5439**
Matrix	Plasma	
Anticoagulant	K_2EDTA	
Assay Volume	100 µL	
Selectivity		
Analyte	Ripretinib	DP-5439
Internal Standard	DP-6246	DP-6977
Matrix Effect (6 spiked matrix lots)	%CV of Average IS Normalized MF: Low concentration 1.4 High concentration 0.7	%CV of Average IS Normalized MF: Low concentration 1.2 High concentration 0.7
Interference	Assay selectivity was confirmed by spiking quality control pools with 2000 ng/mL itraconazole and 2000 ng/mL hydroxyitraconazole and 3500 ng/mL pantoprazole. These QC pools, containing low level of DCC-2618 and DP-5439, were analyzed in replicate in a single batch. the mean % bias at each level was <15.0% and the % CV was ≤ 15.0% for ripretinib and DP-5439	
Hemolytic Effect Evaluation	Acceptable	Acceptable
Carry-Over	Acceptable	Acceptable
Linearity		
Weighting	$1/x^2$	$1/x^2$
Bias at LLOQ	-0.5%	0.5%
Bias above LLOQ	-1.1 to 1.8%	-2.0 to 1.8%
Bioanalytical Range	2.00 - 1000 ng/mL	2.00 - 1000 ng/mL
Precision		
Intra-assay	3.4 to 10 3% (LLOQ); 1.3 to 6.6% (above LLOQ)	3.6 to 7.3% (LLOQ); 1.3 to 5.0% (above LLOQ)
Inter-assay	9.3% (LLOQ); 3.2 to 4.3% (above LLOQ)	5.9% (LLOQ); 2.2 to 3.1% (above LLOQ)

Accuracy		
Intra-assay	-9.0 to 5.0% (LLOQ); -3.2 to 5.0% (above LLOQ)	-2.0 to 0.5% (LLOQ); -2.7 to 2.5% (above LLOQ)
Inter-assay	-1.5% (LLOQ); -2.0 to 3.3% (above LLOQ)	-1.5% (LLOQ); -0.7 to 1.7% (above LLOQ)
Dilution		
Dilution factor: 2x, 5x	Precision: 2.3%, 2.6% Accuracy: -1.7%, -3.0%	Precision: 2.4%, 3.1% Accuracy: -1.5%, -2.5%
Extraction Recovery	Overall 98.8%	Overall 97.9%
Methodology – VDECI1500P1	**Method Performance – LC-MS/MS**	
	Ripretinib	**DP-5439**
Matrix	Plasma	
Anticoagulant	K_2EDTA	
Assay Volume	100 µL	
Selectivity		
Analyte	Ripretinib	DP-5439
Internal Standard	DP-6246	DP-6977
Matrix Effect (6 spiked matrix lots)	%CV of Average IS Normalized MF: Low concentration 5.4 High concentration 0.4	%CV of Average IS Normalized MF: Low concentration 4.8 High concentration 0.5
Hemolytic Effect Evaluation	Acceptable	Acceptable
Carry-Over	Acceptable	Acceptable
Linearity		
Weighting	$1/x^2$	$1/x^2$
Bias at LLOQ	-1.0%	0.2%
Bias above LLOQ	-7.2 to 5.1%	-5.7 to 4.8%
Bioanalytical Range	10.00 - 4000 ng/mL	10.00 - 4000 ng/mL
Precision		
Intra-assay	7.2 to 9.4% (LLOQ); 1.7 to 6.6% (above LLOQ)	3.7 to 5.8% (LLOQ); 1.4 to 4.7% (above LLOQ)
Inter-assay	8.0% (LLOQ); 2.8 to 4.1% (above LLOQ)	5.0% (LLOQ); 2.4 to 3.7% (above LLOQ)
Accuracy		
Intra-assay	4.5 to 5.8% (LLOQ); -3.4 to 4.0% (above LLOQ)	3.6 to 9.8% (LLOQ); 1.3 to 11.4% (above LLOQ)
Inter-assay	5.0% (LLOQ); -2.2 to 3.6% (above LLOQ)	6.3% (LLOQ); 2.6 to 10.0% (above LLOQ)
Dilution		
Dilution factor: 2x, 5x	Precision: 3.8%, 2.9% Accuracy: -0.5%, -10.3%	Precision: 2.3%, 5.6% Accuracy: 3.0%, -4.5%
Extraction Recovery	Overall 85.9%	Overall 83.7%

Source: Bioanalytical method validation reports V1471901P1 and VDECI1500P1

19.3.2 Pharmacometrics Review

19.3.2.1 Population PK analysis

The goal of population PK analysis (popPK) was to develop a population pharmacokinetic (PK) model to assess sources of variability (intrinsic and extrinsic covariates) of ripretinib and its active metabolite DP-5439 in patients.

The population PK model for ripretinib included 350 patients with 5284 quantifiable ripretinib concentrations pooled from studies DCC-2618-01-001 and DCC-2618-03-001. The population PK model for DP-5439 included 350 patients with 5160 quantifiable DP-5439 concentrations. Baseline characteristics of 350 patients in the popPK analysis dataset were provided in Table 25 and Table 26.

The popPK analysis was conducted by the sponsor and evaluated by the reviewer. The PK of ripretinib was characterized by a two-compartment model with linear elimination. The absorption process of ripretinib was described as zero-order drug release followed by first-order absorption with a modest, linear dose-dependent decrease in relative bioavailability (Frel) with increasing dose. The residual error model was described by a proportional and additive error model. Ripretinib concentrations derived from the individual post hoc ripretinib PK parameter estimates from the final ripretinib model were used as input for the development of the model for the metabolite DP-5439. The PK of metabolite DP-5439 was described by a 1-compartment model with linear elimination.

A stepwise covariate modeling approach was implemented to investigate the effects of covariate on ripretinib. The candidate covariate-parameter relationships were added simultaneously to the base model, resulting in the full model. Model covariate relationships were dropped from the full model using a backward elimination method based on a statistical significance level of $p < 0.005$.

Parameter estimates of final model for ripretinib and its metabolite DP-5439 were provided in Table 27 and Table 28. The final model included effects of gender on CL/F as well as an effect of prior gastrectomy status on first-order absorption rate constant (Ka). No signs of model misspecification were identified in the goodness-of-fit plots (Figure 6 and Figure 7). Prediction-corrected visual predictive check showed that the final model adequately described the observed PK profile of ripretinib across different clinical studies (Figure 8 and Figure 9). The effects of all evaluated covariates on the ripretinib and DP-5439 exposure were illustrated in the forest plot (Figure 10).

No clinically meaning effects on the PK of ripretinib and DP-5439 were identified for age (19 to 87 years), sex, race (White, Black, and Asian), body weight (39 to 138.2 kg), tumor type (GIST or other solid tumor), prior gastrectomy, mild to moderate renal impairment (baseline creatinine clearance [CRCL] 30 to <90 mL/min) and mild hepatic impairment (National Cancer Institute [NCI] hepatic. The 95% CIs of the magnitude of the covariate effects on ripretinib and DP-5439 AUC all included 1. There was no effect of prior gastrectomy on the AUC of ripretinib or DP-5439. The post-hoc ripretinib CL were similar between subjects with normal liver function (N=207) and subjects with mild hepatic impairment (N=89) (Figure 11). The post-hoc ripretinib CL were also similar between subjects with normal renal function (N=143) and subjects with mild renal impairment (N=101) and subjects with moderate renal function (N=49) (Figure 12).

Table 25: Baseline Characteristics of Patients in the PK Analysis Dataset (Continuous Variables)

Covariate	**Mean (SD)** **Median [Minimum, Maximum]**		
	Study DCC-2618-01-001 (N = 237)	**Study DCC-2618-03-001 (N = 113)**	**Overall (N = 350)**
Age (y)	59.9 (12.4) 61.0 [19.0, 87.0]	60.0 (11.8) 60.0 [29.0, 82.0]	59.9 (12.2) 60.0 [19.0, 87.0]
Albumin (g/dL)	40.1 (4.90) 41.0 [23.0, 51.0]	39.8 (4.95) 40.0 [21.0, 50.0]	40.0 (4.91) 41.0 [21.0, 51.0]
ALP (IU/L)	110.0 (90.9) 79.0 [27.0, 605.0]	148.0 (182.0) 89.0 [40.0, 1565.0]	122.0 (128.0) 83.0 [27.0, 1565.0]
ALT (IU/L)	22.3 (15.2)	21.7 (15.3)	22.1 (15.2) 18.0 [6.0,

	18.0 [6.0, 119.0]	16.0 [6.00, 89.0]	119.0]
AST (IU/L)	26.6 (17.1) 22.0 [5.0, 143.0]	30.0 (28.5) 23.0 [7.00, 285.0]	27.7 (21.4) 22.0 [5.0, 285.0]
BILI (mg/dL)	0.478 (0.307) 0.400 [0.200, 3.00]	0.444 (0.301) 0.400 [0.200, 2.20]	0.468 (0.305) 0.400 [0.200, 3.00]
BMI (kg/m^2)	26.9 (5.99) 25.8 [13.9, 54.7]	25.2 (5.91) 23.7 [13.5, 46.5]	26.3 (6.01) 25.1 [13.5, 54.7]
BSA (m^2)	1.90 (0.238) 1.89 [1.36, 2.56]	1.83 (0.254) 1.81 [1.30, 2.47]	1.87 (0.245) 1.87 [1.30, 2.56]
CRCL (mL/min)	98.1 (39.1) 91.6 [28.0, 239.0]	93.7 (40.3) 85.2 [29.5, 242.0]	96.7 (39.5) 90.5 [28.0, 242.0]
Normalized CRCL ($mL/min/1.73\ m^2$)	88.9 (32.3) 84.4 [27.5, 238.0]	86.7 (30.7) 84.3 [32.7, 169.0]	88.1 (31.8) 84.4 [27.5, 238.0]
Weight (kg)	78.5 (19.0) 76.3 [39.0, 138.0]	72.9 (19.1) 70.7 [39.2, 133.0]	76.7 (19.2) 74.4 [39.0, 138.0]

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase;

BILI = bilirubin; BMI = body mass index; BSA = body surface area; CRCL = creatinine clearance; N = number of patients; PK = pharmacokinetic; SD = standard deviation.

Source: Applicant's PopPK report, Table 5, Page 32

Table 26: Baseline Characteristics of Patients in the PK Analysis Dataset (Categorical Variables)

Covariate	Category	Study DCC-2618-01-001 (N = 237)	Study DCC-2618-03-001 (N = 113)	Overall (N = 350)
Starting dose	Placebo	0 (0%)	28 (24.8%)	28 (8.0%)
	20 mg BID	4 (1.7%)	0 (0%)	4 (1.1%)
	30 mg BID	4 (1.7%)	0 (0%)	4 (1.1%)
	50 mg BID	11 (4.6%)	0 (0%)	11 (3.1%)
	100 mg BID	12 (5.1%)	0 (0%)	12 (3.4%)
	100 mg QD	6 (2.5%)	0 (0%)	6 (1.7%)
	150 mg BID	6 (2.5%)	0 (0%)	6 (1.7%)
	150 mg QD	181 (76.4%)	85 (75.2%)	266 (76.0%)
	200 mg BID	7 (3.0%)	0 (0%)	7 (2.0%)
	250 mg QD	6 (2.5%)	0 (0%)	6 (1.7%)
Sex	Male	147 (62.0%)	63 (55.8%)	210 (60.0%)
	Female	90 (38.0%)	50 (44.2%)	140 (40.0%)
Race	White	189 (79.7%)	84 (74.3%)	273 (78.0%)
	Black	17 (7.17%)	10 (8.85%)	27 (7.71%)
	Amer. Ind. or AK Native	3 (1.27%)	0 (0.0%)	3 (0.857%)
	Asian	14 (5.91%)	6 (5.31%)	20 (5.71%)
	Other	14 (5.91%)	1 (0.885%)	15 (4.29%)
	Unknown	0 (0.0%)	12 (10.6%)	12 (3.43%)
Tumor type	GIST	184 (77.6%)	113 (100%)	297 (84.9%)

	Melanoma	5 (2.11%)	0 (0.0%)	5 (1.43%)
	Systemic mastocytosis	8 (3.38%)	0 (0.0%)	8 (2.29%)
	Soft tissue sarcoma	2 (0.844%)	0 (0.0%)	2 (0.571%)
	Other solid tumor	38 (16.0%)	0 (0.0%)	38 (10.9%)
ECOG status	0: Fully active	89 (37.6%)	48 (42.5%)	137 (39.1%)
	1: Restricted activity	137 (57.8%)	57 (50.4%)	194 (55.4%)
	2: Only self-care	11 (4.64%)	8 (7.08%)	19 (5.43%)
NCI hepatic impairment category	A = Normal	206 (86.9%)	51 (45.1%)	257 (73.4%)
	B1 = Mild hepatic impairment	27 (11.4%)	62 (54.9%)	89 (25.4%)
	B2 = Mild hepatic impairment	2 (0.844%)	0 (0.0%)	2 (0.571%)
	C = Moderate hepatic impairment	2 (0.844%)	0 (0.0%)	2 (0.571%)
Renal impairment	Normal (CRCL ≥90 mL/min)	126 (53.2%)	52 (46.0%)	178 (50.9%)
	Mild impairment (60 to 89	76 (32.1%)	36 (31.9%)	112 (32.0%)
	Moderate impairment (30 to 59 mL/min)	32 (13.5%)	22 (19.5%)	54 (15.4%)
	Severe impairment (15 to 29 mL/min)	3 (1.27%)	1 (0.885%)	4 (1.14%)
	Unknown (due to missing CRCL)	0 (0.0%)	2 (1.77%)	2 (0.571%)
Gastrectomy	None	194 (81.9%)	100 (88.5%)	294 (84.0%)
	Partial	34 (14.3%)	7 (6.19%)	41 (11.7%)
	Full	3 (1.27%)	3 (2.65%)	6 (1.71%)
	Unknown type	6 (2.53%)	3 (2.65%)	9 (2.57%)

Source: Applicant's PopPK report, Table 6, Page 32

Table 27: Parameter Estimates of the Final PopPK Model for Ripretinib

Parameter	Fixed Effects		BSV CV %		Shrinkage
	Estimate	RSE%	Estimate	RSE%	
Apparent clearance; CL/F (L/h)	12.7	4.0%	53.6%	3.9%	7.0%
Apparent central volume of distribution ; Vc/F (L)	20.4	8.7%	58.2%	17.5%	57.1%
Apparent inter-compartmental clearance; Q/F (L/h)	7.30	3.0%	0 FIXED	N/A	N/A
Peripheral volume of distribution; Vp/F (L)	675	7.2%	1465%	7.3%	26.4%
First-order absorption rate constant; Ka (1/h)	0.0832	2.7%	43.2 %	5.9%	22.3%
Duration of zero-order release; D1 (h)	1.459	6.6%	71.4%	6.6%	38.2%
Frel vs. dose slope (1/mg)	-0.00293	8.8%	N/A	N/A	
D1 ~ high-fat meal fold-change	3.47 FIXED	0 FIXED	N/A	N/A	
Frel ~ high-fat meal fold-change, <100 mg	1.131 FIXED	N/A	N/A	N/A	
Frel ~ high-fat meal fold-change, 100 mg or 150 mg	1.356 FIXED	N/A	N/A	N/A	
Frel ~ high-fat meal fold-change, >150 mg	1.683 FIXED	N/A	N/A	N/A	
CL/F ~ female fractional change	-0.287	14.4%			
Ka ~ prior gastrectomy fractional change	0.230	40.3%			
Proportional residual error (CV %)	41.0%	0.85%			
Additive residual error standard deviation (ng/mL)	29.6	1.9%			

BSV = between-subject variability; CL/F = apparent clearance; CV % = percent coefficient of variation; D1 = duration of zero-order release; Frel = relative bioavailability; Ka = first-order absorption rate constant; N/A = not applicable; Q/F = apparent inter-compartmental clearance; RSE = relative standard error; SD = standard deviation; Vc/F = apparent central volume of distribution; Vp/F = apparent peripheral volume of distribution; vs. = versus.

Source: Applicant's PopPK report, Table 11, Page 42

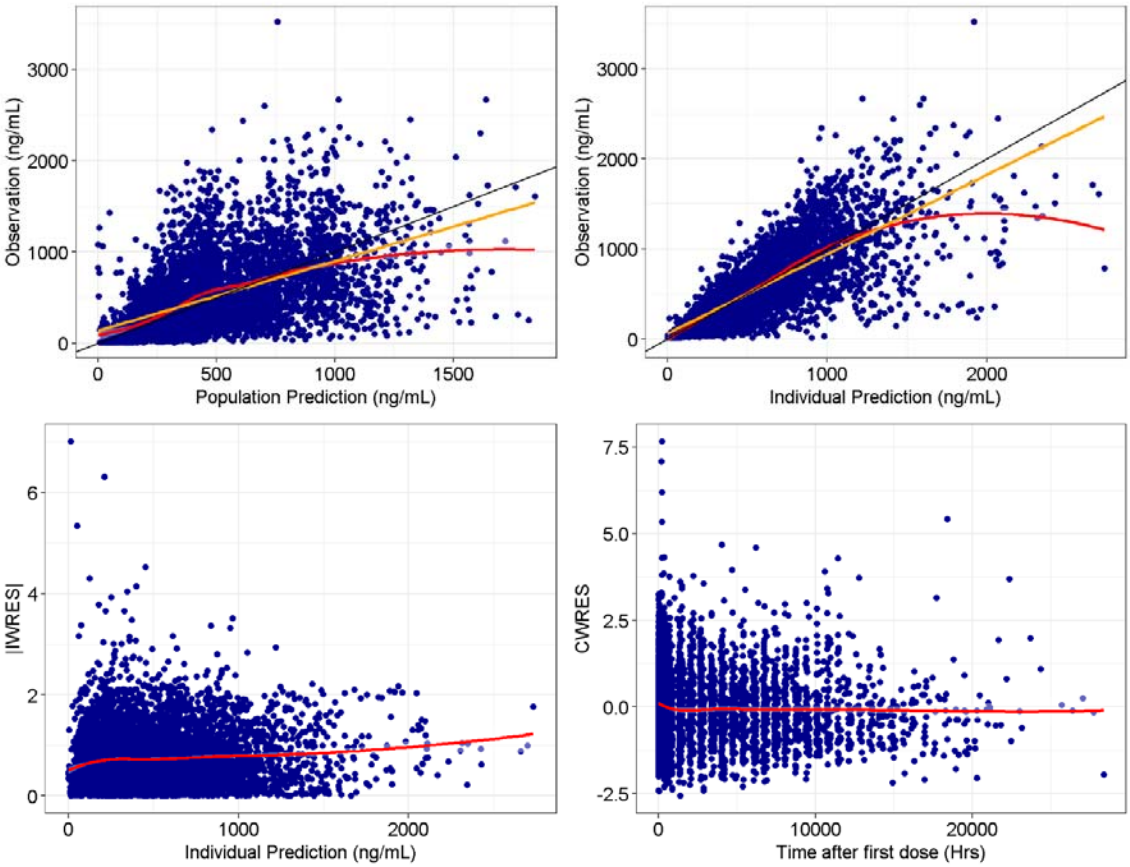
Table 28: Parameter Estimates of the Final PopPK Model for DP-5439

Parameter	Fixed Effects		BSV CV %		Shrinkage
	Estimate	RSE%	Estimate	RSE%	
Apparent clearance; CL_m/F (L/h)	7.29	5.0%	84.8%	4.3%	2.3%
Apparent Oral Central Volume; V_m/F (L)	64.0	5.0%	72.9%	3.8%	15.7%
Proportional residual error (CV %)	40.6%	0.55%	N/A	N/A	
Additive residual error SD (ng/mL)	26.5	2.7%	N/A	N/A	

BSV = between-subject variability; CL_m/F = apparent clearance of metabolite DP-5439; CV % = percent coefficient of variation; N/A = not applicable; RSE = Relative standard error; SD = standard deviation; V_m/F = metabolite volume of distribution.

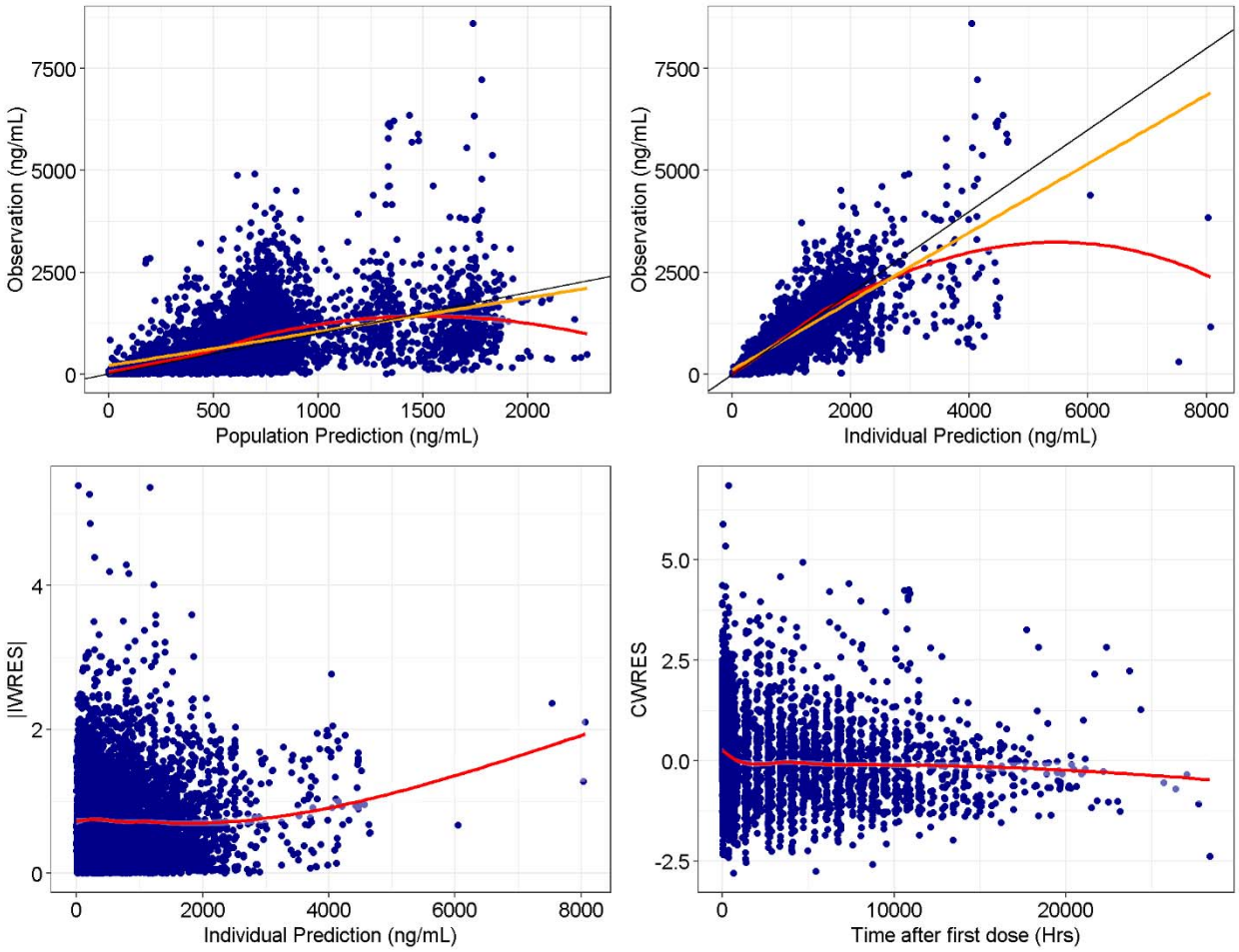
Source: Applicant's PopPK report, Table 12, Page 42

Figure 6: Goodness of Fit Plots of the Final Model for Ripretinib



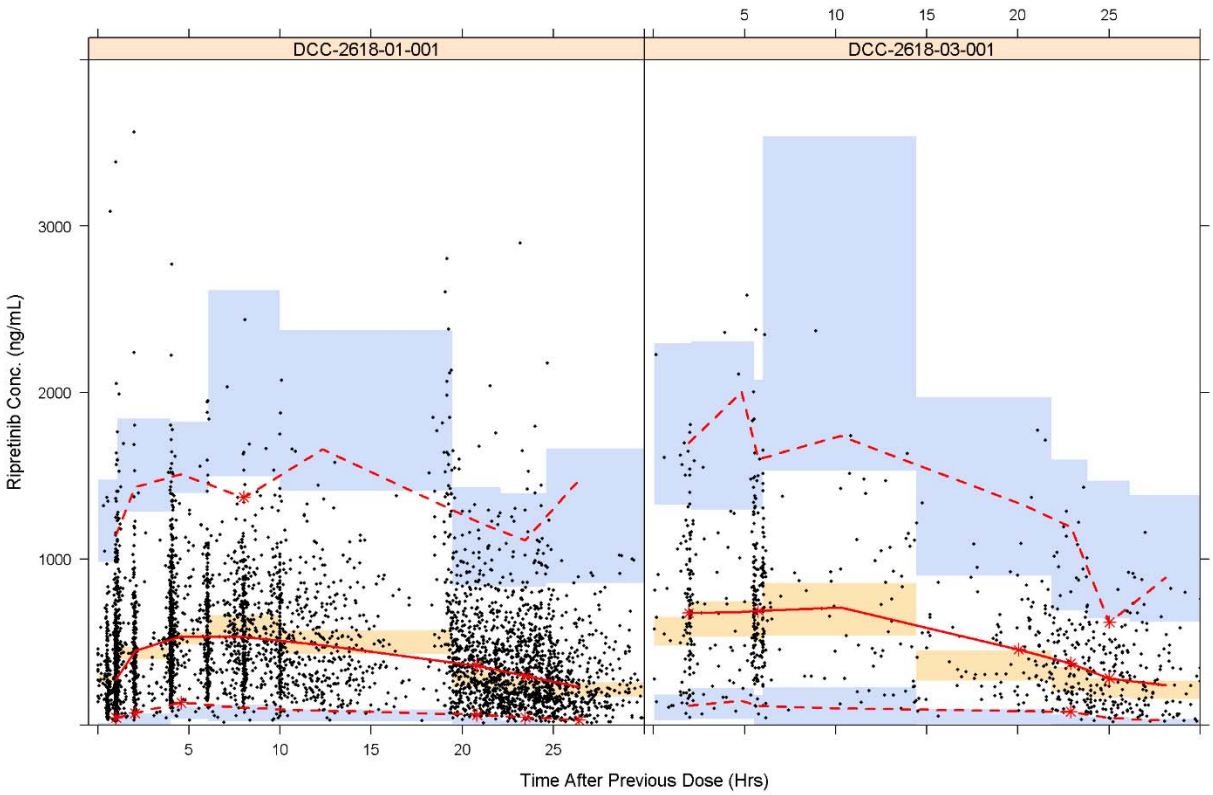
Source: Reviewer's Analysis based on data "dcc-2618-all-poppk-24oct2019.csv"

Figure 7: Goodness of Fit Plots of the Final Model for DP-5439



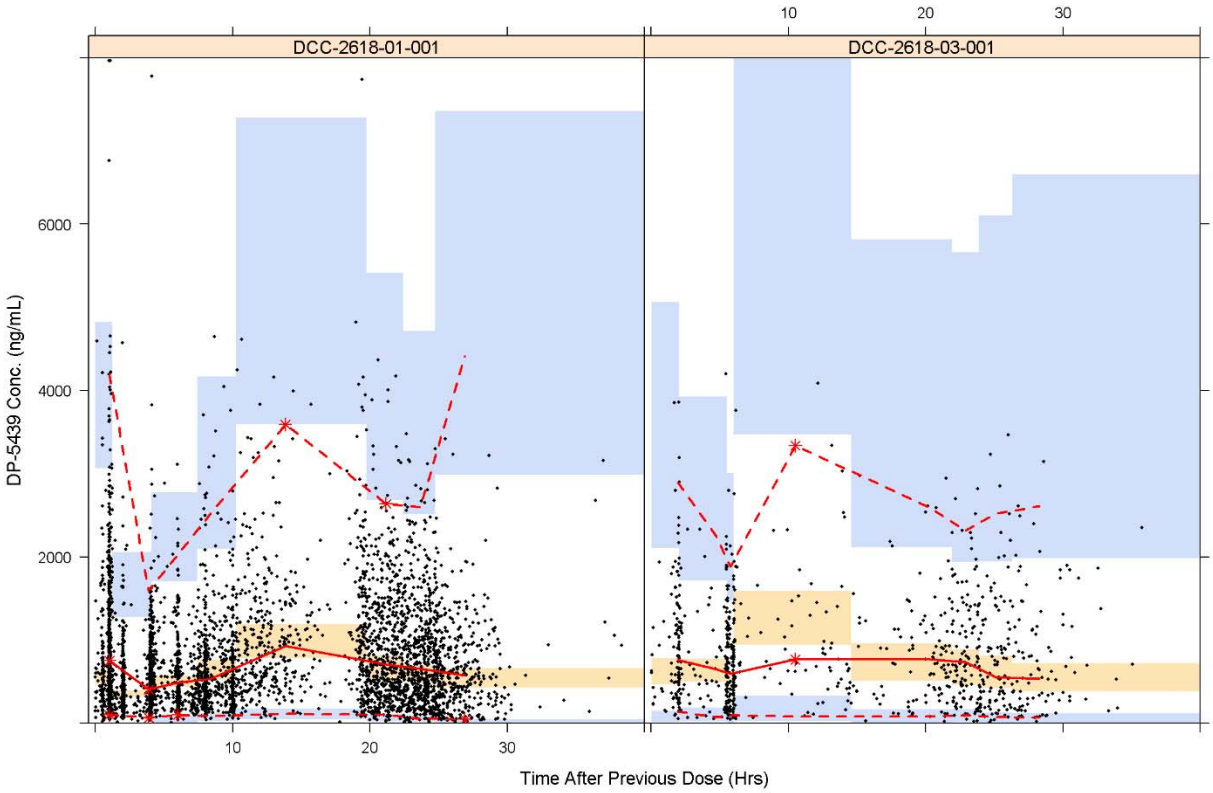
Source: Reviewer's Analysis based on data "dcc-2618-all-poppk-24oct2019_m-0127.csv"

Figure 8: Visual Predictive Checks of Ripretinib Concentration-Time Data Stratified by Clinical Studies.



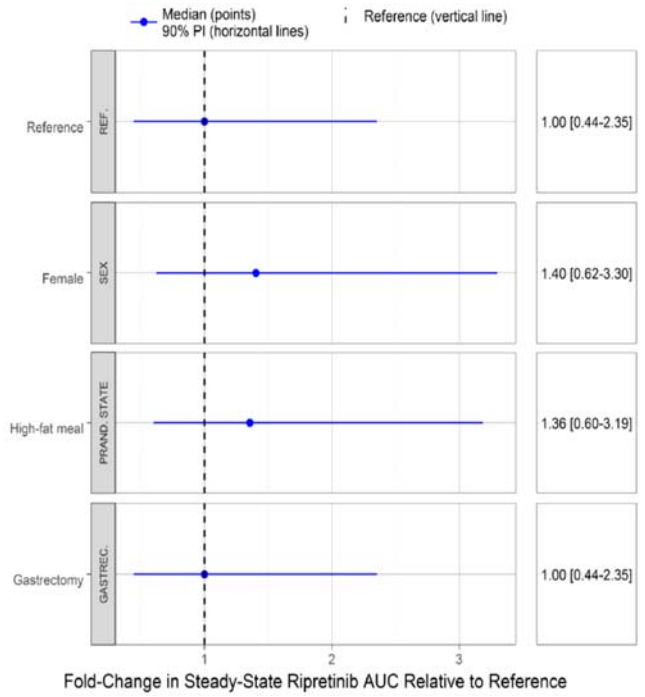
Source: Reviewer's Analysis based on data "dcc-2618-all-poppk-24oct2019.csv"

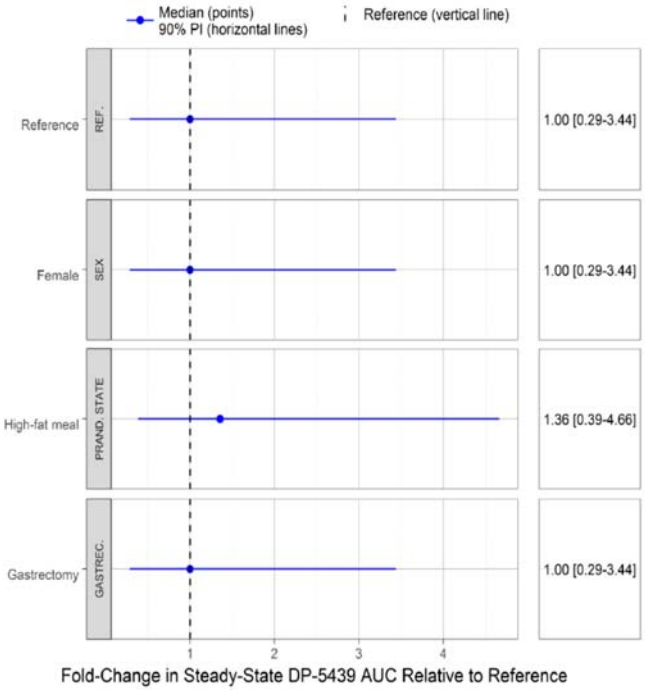
Figure 9: Visual Predictive Checks of DP-5439 Concentration-Time Data Stratified by Clinical Studies.



Source: Reviewer's Analysis based on data "dcc-2618-all-poppk-24oct2019_m-0127.csv"

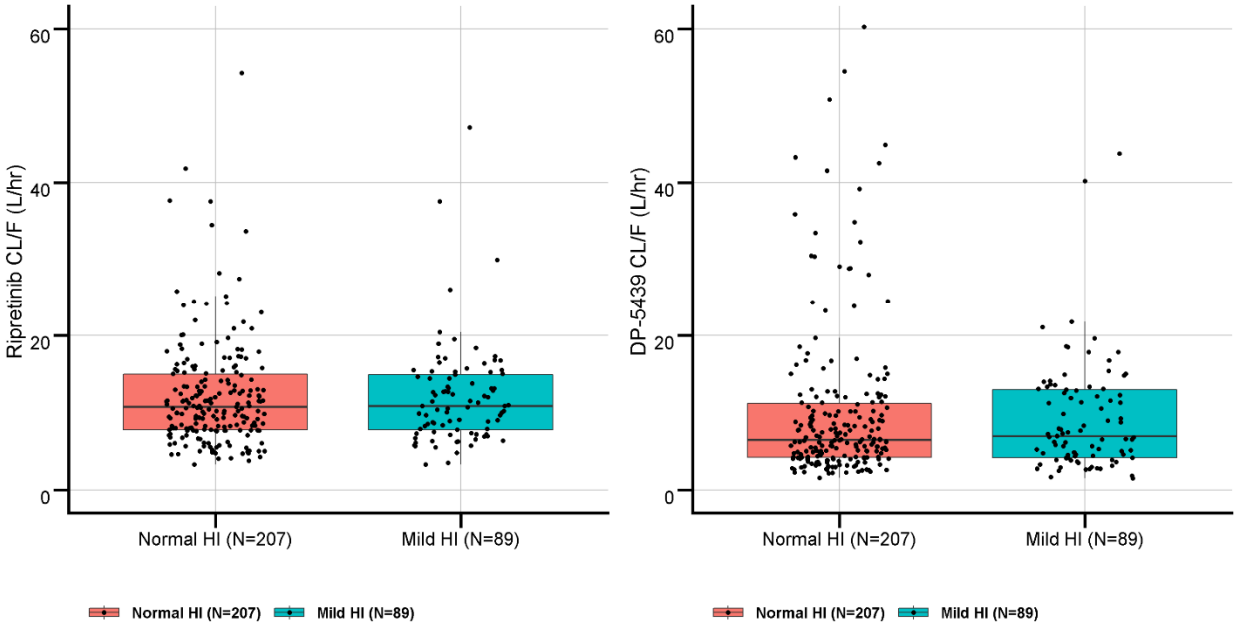
Figure 10: Covariate Effects on Ripretinib Steady-State AUC





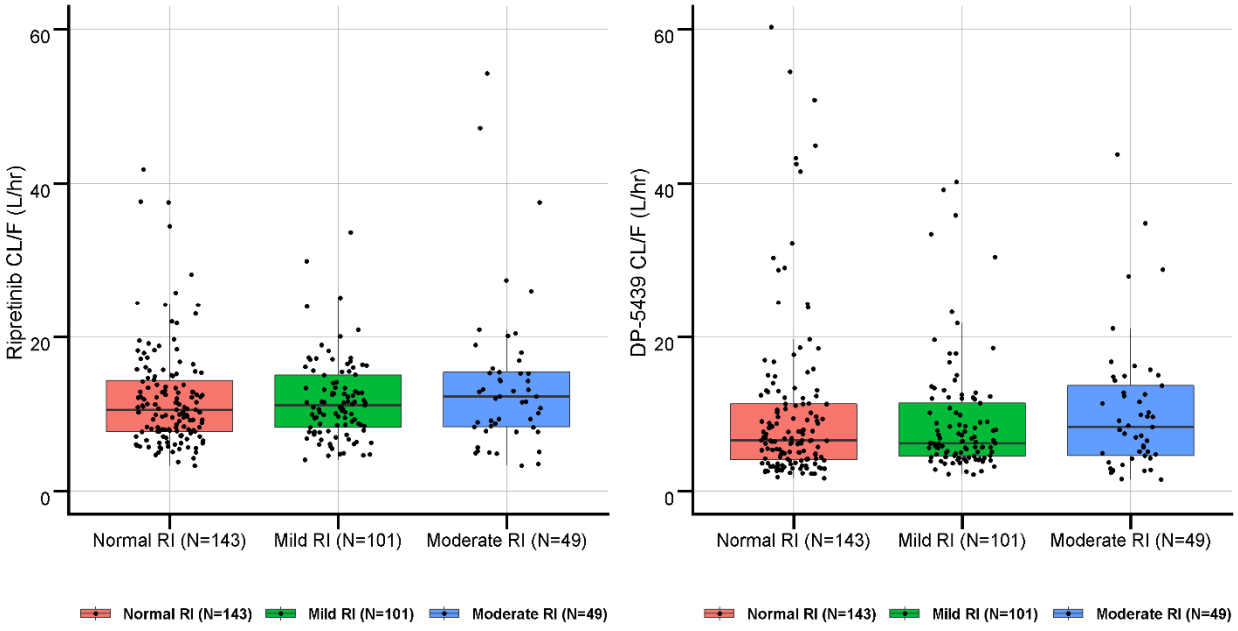
Source: Applicant's Poppk report, Figure 15 and Figure 16

Figure 11: Comparison of Post-hoc CL across Hepatic Function.



Source: Reviewer's Analysis based on data "dcc-2618-all-poppk-24oct2019.csv"

Figure 12: Comparison of Post-hoc CL across Renal Function.



Source: Reviewer's Analysis based on data "dcc-2618-all-poppk-24oct2019.csv"

19.3.2.2 Exposure Response Analysis

1) Methods and Data

Exposure-response analyses were conducted by the applicant to explore the relationship between exposure of ripretinib and efficacy and safety in patients who received ripretinib.

Exposure-efficacy analyses was conducted in 83 patients in the treatment group with evaluable ripretinib and/or DP-5439 exposure and efficacy endpoint from phase 3 study DCC-2618-03-001 (INVICTUS).

Exposure-safety analyses explored the relationship between ripretinib and/or DP-5439 exposure and any grade and grade 3 or higher (Gr3+) occurrence of the following AEs:

- Palmar-plantar erythrodysesthesia syndrome (PPES)
- Hypertension
- Myalgia
- Diarrhea
- Hyperbilirubinemia or increased blood bilirubin

The exposure-safety analyses were conducted in 313 patients including 230 patients from study DCC-2618-01-001 and 83 patients from study DCC-2618-03-001.

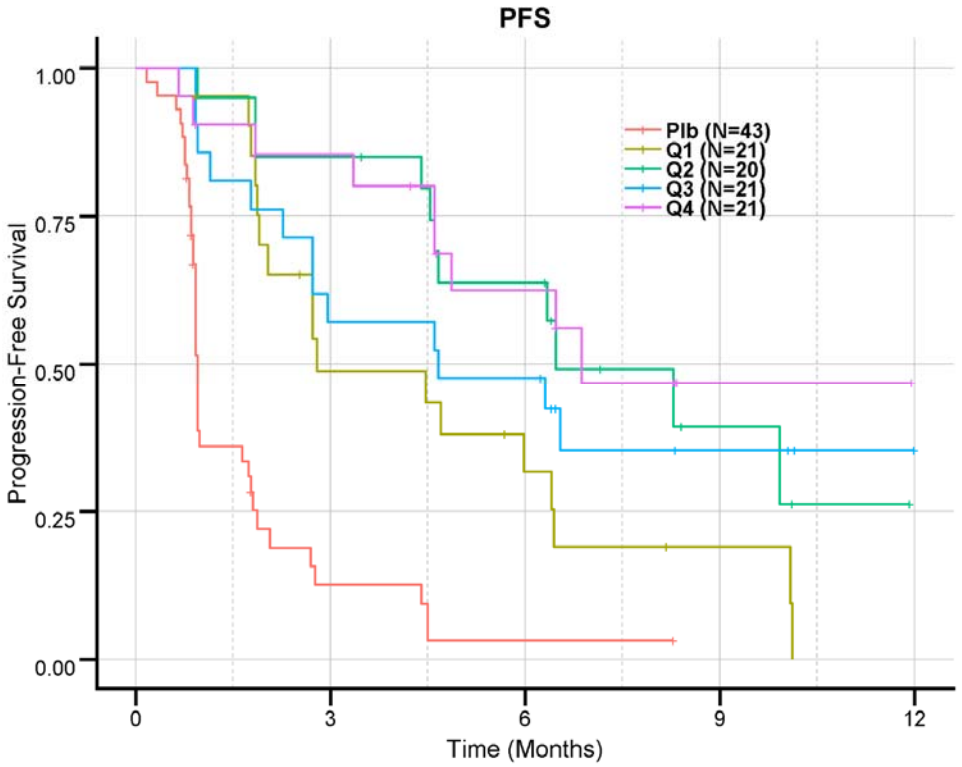
The primary exposure metrics for exposure-efficacy assessment are observed average combined Cmin of ripretinib and DP-5439 up to the time of event (disease progression/death) or censoring. The primary exposure metrics for exposure-safety assessment are observed average combined Cmin of ripretinib and DP-5439 up to the event of first adverse event occurrence or censoring. Graphical quartile analyses were used to investigate the exposure-AE relationships. Cox proportional model was used to evaluate the association between ripretinib exposure and PFS.

2) Exposure-PFS Relationships

Overall, there appears to be a positive trend of exposure-response relationship for PFS with patients with lower exposure (Q1) having lower median PFS than patients with higher exposure (Q2-Q4). The average Cmin up to the time of event (disease progression/death) or censoring is also associated with PFS based on a cox proportional hazard model ($P<0.05$) (Figure 13). However, caution should be exercised when interpreting the results of the exposure-efficacy analysis as it was based on a small sample size with one dosing regimen; the median PFS in the lowest exposure quartile (Q1) is higher than the median PFS in the placebo arm. The baseline covariates across four exposure quartiles in the exposure-ORR analyses appeared to be

imbalanced, but this may be due to small number of subjects in each quartile (Table 29). Mutation status appears to be the only baseline covariate tested to be a significant predictor on PFS; Patients with mutation on KIT exon 9 or those with mutation on PDGFRA, KIT other exons appear to have lower median PFS compared to patients with mutation on KIT exon 11. But such observation may be due to chance with small number of subjects, and the difference is not supported by the known mechanism of action.

Figure 13: Relationship between Ripretinib Exposure and PFS in Patients with GIST Tumor.



Source: Reviewer's Analysis based on data "er-data.xpt"

Table 29: Baseline Covariates across 4 Exposure Quartiles in the Exposure-Efficacy Analyses.

Covariate	Value	Q1	Q2	Q3	Q4
Number of Subjects		21	20	21	21
Age		58 (10.9)	56.5 (9.9)	65 (10.4)	60 (11.4)
Body Weight		64.4 (15.6)	73.5 (18.7)	73 (18.9)	80 (20.6)
ECOG	0	8 (38.1%)	5 (25%)	11 (52.4%)	13 (61.9%)
ECOG	1	11 (52.4%)	13 (65%)	7 (33.3%)	7 (33.3%)
ECOG	2	2 (9.5%)	2 (10%)	3 (14.3%)	1 (4.8%)
Gastrectomy	Full gastrectomy	2 (9.5%)	NA	1 (4.8%)	NA
Gastrectomy	No gastrectomy	15 (71.4%)	19 (95%)	18 (85.7%)	20 (95.2%)

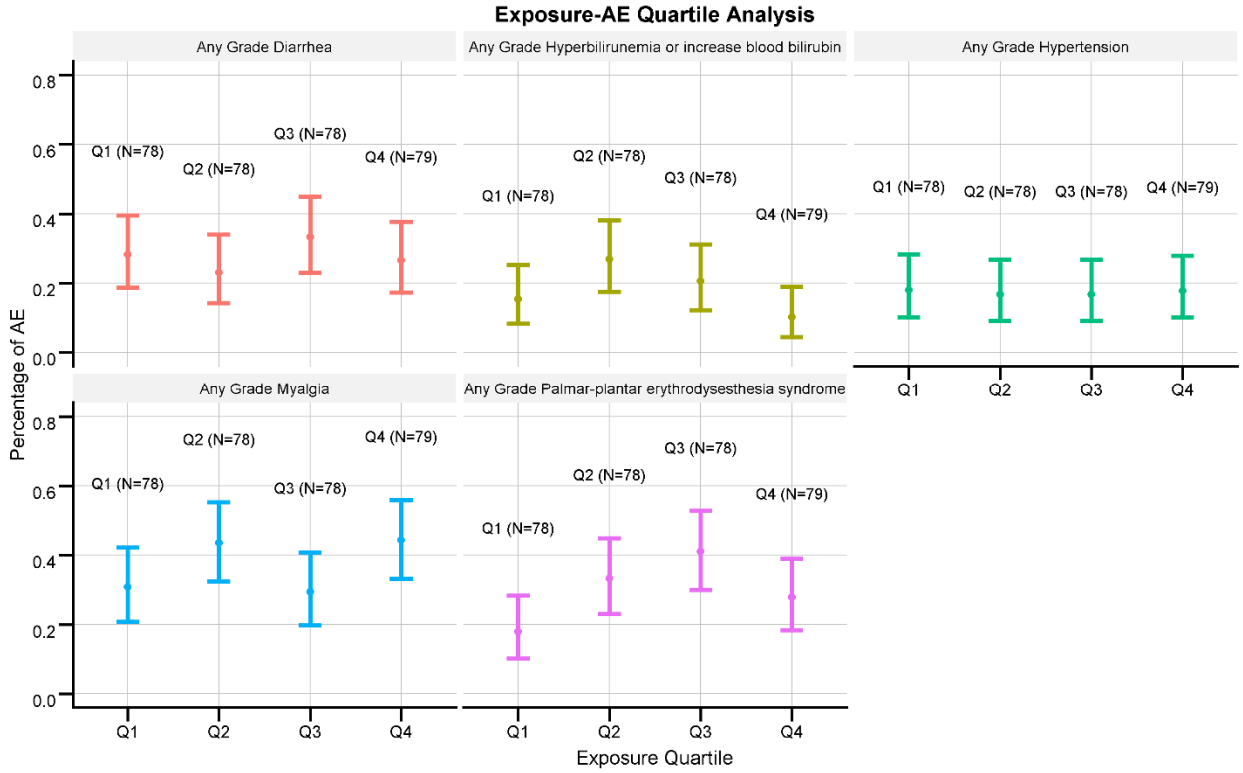
Gastrectomy	Partial gastrectomy	3 (14.3%)	1 (5%)	1 (4.8%)	1 (4.8%)
Gastrectomy	Unknown	1 (4.8%)	NA	1 (4.8%)	NA
Mutation status	KIT exon 11	14 (66.7%)	10 (50%)	13 (61.9%)	10 (47.6%)
Mutation status	KIT exon 9	2 (9.5%)	3 (15%)	5 (23.8%)	4 (19%)
Mutation status	KIT/PDGFRA WT	4 (19%)	NA	NA	3 (14.3%)
Mutation status	PDGFRA, KIT other exons	1 (4.8%)	NA	2 (9.5%)	1 (4.8%)
Mutation status	Unknown	NA	7 (35%)	1 (4.8%)	3 (14.3%)
Race	ASIAN	2 (9.5%)	1 (5%)	1 (4.8%)	NA
Race	BLACK OR AFRICAN AMERICAN	1 (4.8%)	3 (15%)	3 (14.3%)	1 (4.8%)
Race	NOT REPORTED	3 (14.3%)	2 (10%)	1 (4.8%)	2 (9.5%)
Race	OTHER	1 (4.8%)	NA	NA	NA
Race	WHITE	14 (66.7%)	14 (70%)	16 (76.2%)	18 (85.7%)
Gender	F	7 (33.3%)	5 (25%)	10 (47.6%)	15 (71.4%)
Gender	M	14 (66.7%)	15 (75%)	11 (52.4%)	6 (28.6%)
No. of Prior Anticancer Trt	>= 4	13 (61.9%)	9 (45%)	3 (14.3%)	5 (23.8%)
No. of Prior Anticancer Trt	3	8 (38.1%)	11 (55%)	18 (85.7%)	16 (76.2%)

Source: Reviewer's Analysis based on data "er-data.xpt"

3) Exposure-safety Relationships

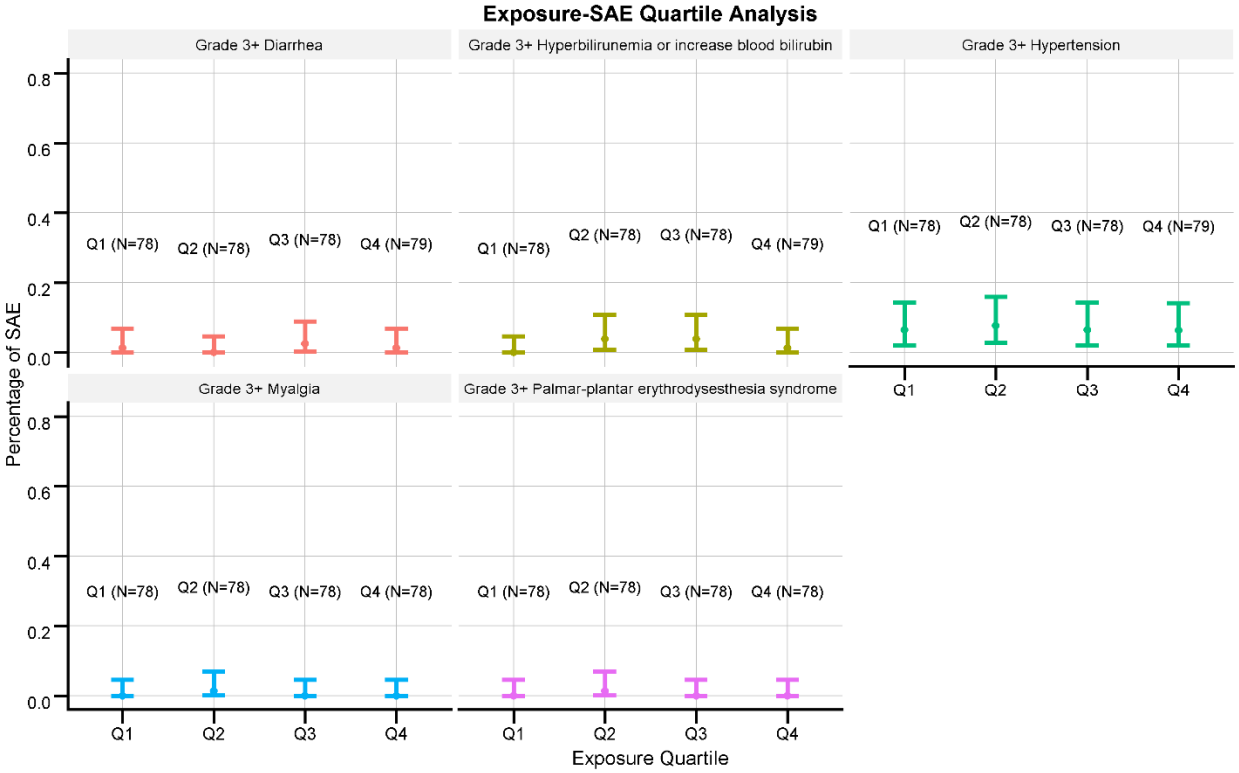
There was a shallow E-R relationship for myalgia any grade and ripretinib C_{trough} as well as palmar-plantar erythrodysesthesia (PPES) any grade and ripretinib C_{trough}. However, graphical quartile analyses do not suggest that combined ripretinib and DP-5439 Cmin are associated with evaluated adverse events of any grade (Figure 14). Moreover, the rate of grade 3+ events for PPES syndrome, hypertension, myalgia, diarrhea and hyperbilirubinemia or increased blood bilirubin are very low and do not appear to be associated with combined ripretinib and DP-5439 Cmin (Figure 15). The baseline covariates across four exposure quartiles in the exposure-safety analyses appeared to be balanced (Table 30).

Figure 14: Relationship between Ripretinib Exposure and Adverse Events of Any Grade.



Source: Reviewer's Analysis based on data "er-data.xpt"

Figure 15: Relationship between Ripretinib Exposure and Adverse Events of Grade 3+.



Source: Reviewer's Analysis based on data "er-data.xpt"

Table 30: Baseline Covariates across 4 Exposure Quartiles in the Exposure-Safety Analyses.

Covariate	Value	Q1	Q2	Q3	Q4
Number of Subjects		78	78	78	79
Age		58.5 (12.1)	58.5 (11.3)	62.5 (11.9)	60 (12.1)
Body Weight		72.5 (16.8)	77.1 (20.1)	79.9 (19)	76.5 (20.1)
ECOG	0	31 (39.7%)	29 (37.2%)	33 (42.3%)	32 (40.5%)
ECOG	1	41 (52.6%)	43 (55.1%)	41 (52.6%)	45 (57%)
ECOG	2	6 (7.7%)	6 (7.7%)	4 (5.1%)	2 (2.5%)
Gastrectomy	Full gastrectomy	3 (3.8%)	1 (1.3%)	NA	1 (1.3%)
Gastrectomy	No gastrectomy	61 (78.2%)	66 (84.6%)	68 (87.2%)	66 (83.5%)
Gastrectomy	Partial gastrectomy	10 (12.8%)	10 (12.8%)	5 (6.4%)	11 (13.9%)
Gastrectomy	Unknown	4 (5.1%)	1 (1.3%)	5 (6.4%)	1 (1.3%)
Mutation status	KIT exon 11	44 (56.4%)	43 (55.1%)	47 (60.3%)	38 (48.1%)
Mutation status	KIT exon 9	6 (7.7%)	11 (14.1%)	15 (19.2%)	17 (21.5%)
Mutation status	KIT/PDGFRA WT	3 (3.8%)	1 (1.3%)	1 (1.3%)	3 (3.8%)
Mutation status	PDGFRA, KIT other exons	6 (7.7%)	3 (3.8%)	3 (3.8%)	10 (12.7%)
Mutation status	Unknown	19 (24.4%)	20 (25.6%)	12 (15.4%)	11 (13.9%)
Race	AMERICAN INDIAN OR ALASKA NATIVE	1 (1.3%)	NA	2 (2.6%)	NA
Race	ASIAN	7 (9%)	7 (9%)	1 (1.3%)	2 (2.5%)
Race	BLACK OR AFRICAN AMERICAN	7 (9%)	5 (6.4%)	9 (11.5%)	3 (3.8%)
Race	NOT REPORTED	3 (3.8%)	2 (2.6%)	2 (2.6%)	1 (1.3%)
Race	OTHER	3 (3.8%)	1 (1.3%)	5 (6.4%)	4 (5.1%)
Race	WHITE	57 (73.1%)	63 (80.8%)	59 (75.6%)	69 (87.3%)
Gender	F	22 (28.2%)	25 (32.1%)	32 (41%)	45 (57%)
Gender	M	56 (71.8%)	53 (67.9%)	46 (59%)	34 (43%)
No. of Prior Anticancer Trt	>= 4	12 (15.4%)	11 (14.1%)	2 (2.6%)	5 (6.3%)
No. of Prior Anticancer Trt	3	13 (16.7%)	7 (9%)	17 (21.8%)	16 (20.3%)
No. of Prior Anticancer Trt	NA	53 (67.9%)	60 (76.9%)	59 (75.6%)	58 (73.4%)

Source: Reviewer's Analysis based on data "er-data.xpt"

19.3.3 KIT or PDGFRA mutations and treatment response

In Study DCC-2618-03-001, KIT and PDGFRA mutation status was retrospectively assessed by a central lab in tumor samples (archived or fresh) of 128 patients (112 evaluable; 73 in the ripretinib arm and 39 in the placebo arm) using a next generation sequencing (NGS)-based assay. In Study DCC-2618-01-001, KIT and PDGFRA mutation information was available for 83 patients from patient's medical history. Over 80% of patients had KIT mutations in both studies, mostly involving exon 11. The number of ripretinib-treated patients and responses (CR or PR) in mutation-defined subgroups is summarized in Table 31. Among patients with KIT mutations in exon 11 (alone or combined with secondary mutations), the ORR was 16.7% (8/47) in Study DCC-2618-03-001 and 8.6% (5/58) in Study DCC-2618-01-001. No objective responses were observed among patients with KIT exon 9 mutations (alone or combined with mutations in KIT exon 17) or in patients with GIST negative for PDGFRA or KIT mutations.

Table 31 :Objective Responses in Patients with KIT- or PDGFRA-mutated GIST in Studies DCC-2618-03-001 and DCC-2618-01-001

	Study DCC-2618-03-001		Study DCC-2618-01-001	
Mutated Gene	**Number of Ripretinib-treated Patients[£], Double-blind Period (N=85)**	**Number of IRR-assessed Responses (N=8)**	**Number of Ripretinib-treated ≥ 4th line GIST Patients, [150 mg QD] (N=83)**	**Number of INV-assessed Responses (N=6)**
KIT (exon number)	63	8	78	6
11	10	0	35	3
11 17	17	4	14	2
11 13	11	2	9	0
11 18	2	1	NA	NA
11 13 17	6	1	NA	NA
11 13 14 17	1	0	NA	NA
9	8	0	13[&]	0
9 17	6	0	2	0
17	2	0	2	1
13	NA	NA	3	0
PDGFRA	3	0	5	0
KIT and PDGFRA Wild Type	7	0	0	0
Unknown *	12	0	0	0

Source: Reviewer exploratory analysis. KIT reference sequences: NM_000222 and NP_000213.1. £The frequency of KIT mutations was similar between arms. No responses (CR or PR) were observed in the placebo arm. & One patient had a PTEN mutation identified. * Unknown = Not available (N=11) or not done (N=1).

Although subgroups are too small to draw conclusions, additional exploratory analysis of PFS in selected KIT mutation-defined subgroups suggested generally consistent outcomes compared to the ITT population (Table 32) including longer median PFS among patients with KIT exon 9 mutation positive tumors who were treated with ripretinib (though less than in ripretinib-treated patients with exon 11 mutations), as compared to the placebo control.

Table 32: Exploratory analysis of Progress-Free survival based on IRR in Double-blind Period by KIT mutation-defined Subgroups in Study DCC-2618-03-001

KIT Mutated Exon(s)	Ripretinib (N)	Placebo (N)	Kaplan-Meier Estimates of PFS (weeks) Median (95%CI)		P (Log-Rank test)
			Ripretinib (N=85)	Placebo (N=44)	
11 (alone or combined[&])	47	28	28.0 (19.7-43.9)	4.1 (3.7-8.0)	<0.0001
9 (alone or combined[&])	14	6	11.9 (8.0-28.9)	4.1 (0.9-12.1)	0.004
Status unknown	12	5	28.1 (7.7-29.9)	4.1 (4.1-19.6)	0.002
KIT and PDGFRA Wild Type	7	3	26.0 (8.7-NE)	9.0 (4.0-NE)	0.45

Source: Reviewer exploratory analysis. KIT reference sequences: NM_000222 and NP_000213.1. [&] "Combined" includes patients with GIST positive for KIT mutations in exons other than 11 or 9; NE: Not estimable.

19.4. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:

FDA conducted no additional safety assessments not already included in this review.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Elizabeth Spehalski	DHOT	Section: 5	**Select one:** X Authored X Approved
	Signature: Elizabeth I. Spehalski -S Digitally signed by Elizabeth I. Spehalski -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0012272551, cn=Elizabeth I. Spehalski -S Date: 2020.05.13 09:59:02 -04'00'			
Nonclinical Team Leader	Matthew Thompson	DHOT	Section: 5	**Select one:** ___ Authored X Approved
	Signature: Matthew D. Thompson -S Digitally signed by Matthew D. Thompson -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001270689, cn=Matthew D. Thompson -S Date: 2020.05.13 15:27:18 -04'00'			
Nonclinical Team Division Director	John Leighton	DHOT	Section: 5	**Select one:** ___ Authored X Approved
	Signature: John K. Leighton -S Digitally signed by John K. Leighton -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300085260, cn=John K. Leighton -S Date: 2020.05.13 10:03:42 -04'00'			
Clinical Pharmacology Reviewer	Hisham Qosa	OCP/DCP II	Sections: 6 and 19.3	**Select one:** X Authored X Approved
	Signature: Hisham Qosa -S (Affiliate) Digitally signed by Hisham Qosa -S (Affiliate) DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001883898, cn=Hisham Qosa -S (Affiliate) Date: 2020.05.12 13:00:01 -04'00'			
Clinical Pharmacology Team Leader	Hong Zhao	OCP/DCP II	Sections: 6 and 19.3	**Select one:** X Authored X Approved
	Signature: Hong Zhao -S Digitally signed by Hong Zhao -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Hong Zhao -S, 0.9.2342.19200300.100.1.1=1300136450 Date: 2020.05.13 13:22:12 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Pharmacometrics Reviewer	Youwei Bi	OCP/DPM	Sections: 6 and 19.3	**Select one:** X Authored X Approved
	Signature: Youwei Bi -S Digitally signed by Youwei Bi -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Youwei Bi -S, 0.9.2342.19200300.100.1.1=2001767281 Date: 2020.05.12 13:15:56 -04'00'			
Pharmacometrics Team Leader	Jiang Liu	OCP/DPM	Sections: 6 and 19.3	**Select one:** X Authored X Approved
	Signature: Jiang Liu -S Digitally signed by Jiang Liu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jiang Liu -S, 0.9.2342.19200300.100.1.1=2000348510 Date: 2020.05.12 14:09:08 -04'00'			
Pharmacogenomics Reviewer	Jielin Sun	OCP/DTPM	Sections: 6 and 19.3	**Select one:** X Authored X Approved
	Signature: Jielin Sun -S Digitally signed by Jielin Sun -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jielin Sun -S, 0.9.2342.19200300.100.1.1=2002164321 Date: 2020.05.13 15:56:11 -04'00'			
Pharmacogenomics Team Leader	Rosane Charlab Orbach	OCP/DTPM	Sections: 6 and 19.3	**Select one:** X Authored X Approved
	Signature: Rosane Charlaborbach -S Digitally signed by Rosane Charlaborbach -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300436672, cn=Rosane Charlaborbach -S Date: 2020.05.12 13:02:02 -04'00'			
Clinical Pharmacology Division Director	NAM Atiqur Rahman	OCP/DCP II	Sections: 6 and 19.3	**Select one:** X Authored X Approved
	Signature: Nam A. Rahman -S Digitally signed by Nam A. Rahman -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Nam A. Rahman -S, 0.9.2342.19200300.100.1.1=1300072597 Date: 2020.05.12 13:21:39 -04'00'			
Clinical Reviewer	Leslie Doros	DO3	Sections: 1, 2, 3, 4.1, 7, 8.1, 8.4, 11, 13, 19.1, 19.2	**Select one:** X Authored X Approved
	Margaret Thompson	DO3	Sections: 1, 8.2, 8.4, 11	**Select one:** X Authored X Approved
	Signature: Margaret Thompson -S Digitally signed by Margaret Thompson S DN: c=US o=U S Government ou=HHS ou=FDA ou=People 0 9 2342 19200300 100 1 1=2001774060 cn=Margaret Thompson S Date: 2020 05 12 12:57:05 04'00' Leslie Doros -S Digitally signed by Leslie Doros -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Leslie Doros -S, 0.9.2342.19200300.100.1.1=2000647874 Date: 2020.05.14 16:28:58 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Team Leader	Lola Fashoyin-Aje	DO3	Sections: 1, 2, 3, 4.1, 7, 8, 11, 13, 19.1, 19.2	**Select one:** X Authored X Approved
	Signature: Refer to final assessment aid			
Statistical Reviewer	Sirisha Mushti	OB/DBV	Sections: 1, 7, 8.1, 8.3, 8.4	**Select one:** X Authored X Approved
	Signature: Sirisha Mushti -S Digitally signed by Sirisha Mushti -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Sirisha Mushti -S, 0.9.2342.19200300.100.1.1=2001315241 Date: 2020.05.12 13:19:52 -04'00'			
Statistical Team Leader	Lisa Rodriguez	OB/DBV	Sections: 1, 7, 8.1, 8.3, 8.4	**Select one:** ___ Authored X Approved
	Signature: Lisa R. Rodriguez -S Digitally signed by Lisa R. Rodriguez -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001011155, cn=Lisa R. Rodriguez -S Date: 2020.05.12 13:10:02 -04'00'			
Acting Division Director (OB)	Shenghui Tang	OB/DBV	Sections: 1, 7, 8.1, 8.3, 8.4	**Select one:** ___ Authored X Approved
	Signature: Shenghui Tang -S Digitally signed by Shenghui Tang -S DN: c=US o=U S Government ou=HHS ou=FDA ou=People cn=Shenghui Tang -S 0 9 2342 19200300 100 1 1=1300224175 Date: 2020 05 14 16 42:36 -04'00'			
Associate Director for Labeling	Stacy S. Shord, Pharm.D.	OOD/IO	Section 11	**Select one:** ___Authored X Approved
	Signature: Stacy Shord -S Digitally signed by Stacy Shord -S DN: c US o U S Government ou HHS ou FDA ou People cn Stacy Shord -S 0.9.2342.19200300.100.1.1 2000356537 Date: 2020 05 15 08:32:38 -04 00			
Cross-Disciplinary Team Leader (CDTL)	Lola Fashoyin-Aje	DO3	Authored Sections: 1 Approved Sections: All	**Select one:** X Authored X Approved
	Signature: Refer to final assessment aid			
Deputy Division Director (Clinical)	Lola Fashoyin-Aje	DO3	Sections: All	**Select one:** ___ Authored X Approved
	Signature: Refer to final assessment aid			

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LEAH S HER
05/15/2020 11:54:47 AM

IBILOLA A FASHOYIN-AJE
05/15/2020 01:40:17 PM

MARC R THEORET
05/15/2020 02:42:24 PM