16 September 2021
EMA/CHMP/555164/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Qinlock

International non-proprietary name: ripretinib

Procedure No. EMEA/H/C/005614/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Qinlock
applicant:	Deciphera Pharmaceuticals (Netherlands) B.V. Atrium Building Floor 4th Strawinskylaan 3051 1077ZX, Amsterdam NETHERLANDS
Active substance:	RIPRETINIB
International Non-proprietary Name/Common Name:	ripretinib
Pharmaco-therapeutic group (ATC Code):	(L01EX19)
Therapeutic indication(s):	Qinlock is indicated for the treatment of adult patients with advanced gastrointestinal stromal tumour (GIST) who have received prior treatment with three or more kinase inhibitors, including imatinib.
Pharmaceutical form(s):	Tablet
Strength(s):	50 mg
Route(s) of administration:	Oral use
Packaging:	bottle (HDPE)
Package size(s):	30 tablets and 90 tablets

List of abbreviations

Abbreviation	Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
Ae	amount of drug excreted
AECI	Adverse Events of Clinical Importance
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AST	Aspartate Transaminase
ATR	Attenuated total reflection
AUC	Area Under the Concentration-Time Curve
BCRP	Breast Cancer Resistance Protein
BID	Twice Daily
BICR	Blinded Independent Central Review
BMI	Body Mass Index
BSEP	Bile Salt Export Pump
C1D1	Cycle 1 Day 1
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CL/F	Apparent Systemic Clearance
CLr	Renal Clearance
Cmax	Maximum Observed Concentration
Cmin	Trough Concentration
CMQ	Customised MedDRA Query
CNS	Central Nervous System
CQAs	Critical quality attributes
CrCL	Creatinine Clearance
COMP	Committee for Orphan Medicinal Products
CPK	Creatine Phosphokinase
CPPs	Critical process parameters
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV%	Percent Coefficient of Variation
CYP	Cytochrome P450
DCR	Disease Control Rate
DDI	Drug-Drug Interaction
DLT	Dose-Limiting Toxicity
DoE	Design of experiments
DOR	Duration of Response
DSC	differential scanning calorimetry
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC QLQ C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30 Item
EMA	European Medicines Agency

Abbreviation	Definition
EOT	End-of-Treatment
E-R	Exposure-Response
EQ-5D-5L	Euroqol 5 Dimension 5 Level
FDA	Food and Drug Administration
Fe	Percentage of drug excreted
FIH	First-In-Human
FMEA	Failure mode effect analysis
Frel	Relative Bioavailability
FTIR	Fourier-transform infrared spectroscopy
GeoCV%	Percent Geometric Coefficient of Variation
GIST	Gastrointestinal Stromal Tumour
HDPE	high-density polyethylene
hERG	Human Ether-A-Go-Go Related Gene
HPLC	High performance liquid chromatography
HPMCAS	Hypromellose Acetate Succinate
HR	Hazard Ratio
HR	Heart rate
HS-GC	Headspace gas chromatography
IC20	20% Maximal Inhibitory Concentration
IC50	Half Maximal Inhibitory Concentration
ICH	International conference on harmonisation
INR	Prothrombin International Normalised Ratio
IPC	In-process controls
IRR	Independent Radiologic Review
IS	Internal standard
ISS	Integrated Safety Summary
ISR	Incurred sample reanalysis
ITT	Intention-to-Treat
IV	Intravenous
IUD	Intrauterine Device
K_2EDTA	Dipotassium Ethylenediaminetetraacetic Acid
Ka	First-Order Absorption Rate Constant
KIT	Proto-Oncogene Receptor Tyrosine Kinase
LC-MS/MS	Liquid Chromatography with Tandem Mass Spectrometry/Mass Spectrometry
LDPE	Low-density polyethylene
LOD	Limit of detection
LOT	Line of Therapy
LSM	Least Squares Means
LVEF	Left Ventricular Ejection Fraction
M:P	Metabolite-to-Parent Ratio
MAA	Marketing Authorisation Application
MATE	Multidrug and Toxin Extrusion Protein
MDR1	Multi-Drug Resistance-1
MedDRA	Medical Dictionary for Regulatory Activities
mPFS	Median Progression-Free Survival
mRECIST	Modified Response Evaluation Criteria in Solid Tumours
MTD	Maximum Tolerated Dose

Abbreviation	Definition
MUGA	Multigated Acquisition
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
NCI	National Cancer Institute
NDA	New Drug Application
NE	Not estimable
NMT	Not more than
OAT	Organic Anion Transporter
OATP	Organic Anion Transporting Polypeptide
OCT	Organic Cation Transporter
ODWG	Organ Dysfunction Working Group
ORR	Objective Response Rate
OS	Overall Survival
PD	Pharmacodynamic(s)
PDGFRA	Platelet-Derived Growth Factor Receptor Alpha
PE	Polyethylene
PFS	Progression Free Survival
P-gp	P-Glycoprotein
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic(s)
PP	Polypropylene
PPES	Palmar-Plantar Erythrodysaesthesia
PPI	Proton Pump Inhibitor
PR	Partial Response
PS	Performance Status
QbD	Quality by Design
QC	Quality Control
QD	Once Daily
QOL	Quality of Life
QTc	QT Interval Corrected for Heart Rate
QTcF	QTc By the Fridericia Method
ΔQTcF	Change from Baseline in The QTcF
QTPP	quality target product profile
RECIST	Response Evaluation Criteria in Solid Tumours
RNA	Ribonucleic Acid
RP-UPLC	Reverse phase ultra-performance liquid chromatography
RP2D	Recommended Phase 2 Dose
RSABE	Reference-Scaled Bioequivalence
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SAWP	Scientific Advice Working Party
SCC	Squamous Cell Carcinoma
SCS	Summary of Clinical Safety
SD	Standard Deviation
SDI	Spray-dried intermediate
SM	Systemic Mastocytosis
SmPC	Summary of Product Characteristics

Abbreviation	Definition
SMQ	Standardised MedDRA Query
SOC	System Organ Class
t½	Terminal Elimination Phase Half-Life
TBL	Total Bilirubin
TEAE	Treatment-Emergent Adverse Event
TGA	Thermogravimetric analysis
TKI	Tyrosine Kinase Inhibitor
tmax	Time to Maximum Observed Concentration
TTR	Time to Response
TTP	Time to Tumour Progression
ULN	Upper Limit of Normal
US	United States
USP	United States Pharmacopeia
UV	Ultraviolet
vs.	Versus
Vc/F	Apparent Central Volume of Distribution
Vz/F	Apparent Volume of Distribution Associated with the Terminal Phase
XRPD	X-ray powder diffractometry

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Background information on the procedure

1.1. Submission of the dossier

The applicant Deciphera Pharmaceuticals (Netherlands) B.V. submitted on 12 September 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Qinlock, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 March 2020.

Qinlock, was designated as an orphan medicinal product EU/3/17/1936 on 12 October 2017 in the following condition: Treatment of gastrointestinal stromal tumours.

The applicant applied for the following indication: <Invented name> is a kinase inhibitor indicated for the treatment of adult patients with advanced gastrointestinal stromal tumour (GIST) who have received prior treatment with two or more kinase inhibitor therapies.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Qinlock as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website:

https://www.ema.europa.eu/en/medicines/human/EPAR/ Qinlock

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) *P/0122/2020* on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

New active Substance status

The applicant requested the active substance ripretinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Protocol assistance

The applicant received the following Protocol Assistance on the development of ripretinib for treatment of patients with advanced gastrointestinal stromal tumours (GIST) from the CHMP:

Date	Reference	SAWP co-ordinators
22 March 2018	EMEA/H/SA/3764/1/2018/PA/III	Dr Daniel O'Connor, Dr Alexandre Moreau
26 March 2020	EMEA/H/SA/3764/2/2020/PA/III	Ms Blanca García-Ochoa Martín, Dr Serena Marchetti

The Protocol assistance pertained to the following quality, non-clinical, and clinical aspects:

- The proposed designation of three starting materials;
- The completed and planned non-clinical studies to support an MAA;
- The overall approach to characterise the metabolism and excretion of ripretinib and its metabolites considering difficulties in developing a suitable radiolabelled formulation of ripretinib;
- The overall clinical programme and expected safety database to support MAA

The appointed co-rapporteur had no such prominent role in protocol assistance relevant for the indication subject to the present application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: Blanca Garcia-Ochoa

The application was received by the EMA on	12 September 2020
The procedure started on	1 October 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	22 December 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	24 December 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	5 January 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	28 January 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	23 April 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	1 June 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to	10 June 2021

CHMP during the meeting on	
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	24 June 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	17 August 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	1 September 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Qinlock on	16 September 2021
The CHMP adopted a report on similarity of Qinlock with Ayvakyt authorised orphan medicinal product(s) on	16 September 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The applicant is seeking full approval for ripretinib with the following target indication:

Qinlock is indicated for the treatment of adult patients with advanced gastrointestinal stromal tumour (GIST) who have received prior treatment with three or more kinase inhibitors, including imatinib.

2.1.2. Epidemiology

Gastrointestinal stromal tumour, GIST, is a rare sarcoma, however the most common malignant mesenchymal tumour of the gastrointestinal tract. It arises from the interstitial cells of Cajal. The most common primary site being the gastric GIST, but it can occur throughout the gastrointestinal tract (Aubin, 2011, Miettinen and Lasota, 2006). There is a slight prevalence in males. The median age is around 60–65 years, with a wide range. Occurrence in children is very rare. GIST represents approximately 0.1% to 3.0% of all GI malignancies (Nilsson et al, 2005) with annual incidences between 4.3 and 22 per million population worldwide. Most studies report annual incidences of 10 to 15 per million in European countries. For localized, potentially resectable disease, initial treatment includes surgery, followed by adjuvant therapy with imatinib for patients with increased risk of recurrence due to poor prognostic factors, such as mitotic rate, tumour size and tumour site (gastric GISTs have a better prognosis than small bowel or rectal GISTs). Tumour rupture is an additional adverse prognostic factor and should be recorded, regardless of whether it took place before or during surgery.

2.1.3. Biologic features

GISTs are primarily characterised by gain-of-function mutations in proto-oncogene proteins, KIT (CD117) or PDGFRA. The majority of GISTs (80% to 85%) harbour primary driver mutations in the KIT gene (~75% of cases), or PDGFRA (~10% of cases) and these may affect the juxta-membrane, extracellular, or catalytic kinase domains (in-frame deletions, insertions, or missense mutations (Emile, 2011, Antonescu, 2011). Certain types of mutations are reflected in response on known therapies. At presentation, mutations in the KIT gene are usually found in exon 9 or 11. Primary mutations in exon 11 disrupt the auto inhibited form of the kinase, and mutations in exon 9 increase receptor dimerization, often requiring an increase in treatment dosage of imatinib. High-dose imatinib in patients with exon 9 mutations may improve progression-free survival (PFS) but has no reported effect on overall survival (OS) (MetaGIST, 2010). PDGFRA exhibits more rarely primary mutations (exons 18, 12 and 14). Exon 18 mutations occur in approximately 6% of GIST, and the most frequent mutation is a substitution in exon 18 D842V (Cassier et al, 2012; Yoo et al, 2016a), which confers resistance to imatinib. A small percentage (10-15%) of GISTs are classified as KIT/PDGFRA wild-type (WT) due to the absence of driver mutations in either KIT or PDGFRA (Kee 2012; Demetri, 2007). The largest subgroup of wild-type GIST is characterised by deficiencies in the succinate dehydrogenase (SDH) complex and, in addition, activating BRAF mutation has been detected in a small percentage of GISTs.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Most tumours are of gastric origin (67.3%), followed by small intestine (15.4%), mesentery (5.8%), rectum and colon (5.8%), esophagus (3.8%), and the ovary (1.9%). Gastrointestinal bleeding is the most common clinical presentation of GISTs, but other features may include intestinal obstruction, abdominal pain, perforation, or a palpable pelvic mass, which may be incidentally detected during a gynecological, urological, or endoscopic/radiological procedure or surgery. After patients display symptoms or an asymptomatic mass is detected, GISTs are usually diagnosed by CT, MRI, PET scan endoscopy or endoscopic ultrasonography techniques. Primary site for metastasis is the liver.

Pathologically, the diagnosis of GIST relies on morphology and immunohistochemistry. In addition, inclusion of mutational analysis in the diagnostic work-up of all GISTs is considered standard practice. Mutational analysis has a predictive value for sensitivity to molecular-targeted therapy. Prognosis varies according to tumour size, mitotic rate, location, and mutation status. In general, tumours of <2 cm are considered of low metastatic risk, whereas larger tumours carry more risk, particularly if they display of a higher mitotic rate (Casali, 2018). GIST located in the stomach is typically of a lower risk compared to intestinal GIST. Mutational status has not been incorporated in any risk classification at present (ESMO 2018) although, mutation status has been shown to carry some correlation with prognosis.

2.1.5. Management

For localized, potentially resectable disease, initial treatment includes surgery, followed by adjuvant therapy with imatinib for patients with increased risk of recurrence due to poor prognostic factors. Adjuvant treatment with imatinib for 3 years was associated with a relapse-free survival (RFS) and OS advantage in comparison with 1 year of adjuvant therapy in high-risk patients in a randomised trial. Data have shown that patients with tumours harbouring the KIT exon 9 mutation have significantly better PFS on a higher dose level, i.e. 800mg daily, which is therefore held as standard treatment (Zalcberg JR, 2005).

Although imatinib have a great therapeutic effect on GIST patients, acquired resistance to imatinib occurs in a median treatment period of less than 2 years (C.D. Blanke, 2008, J. Verweij, 2004), having a 60% response rate and median PFS of 18 to 24 months (Demetri et al, 2002; Blanke et al, 2008).

There are 3 types of disease progression due to resistance seen with imatinib-therapy:

- Primary resistance occurs in about 10% to 15% of patients that do not respond to therapy or achieve disease stabilisation within the first 3 to 6 months of treatment
- Acquired secondary resistance occurs after about 2 years and usually results from secondary KIT mutations.
- Disease progression due to PK resistance occurs in up to 30% of GIST patients. PK resistance results from inadequate drug exposure due to 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).

Sunitinib (authorized for 2nd line GIST) and regorafenib (authorized for 3rd line GIST) are less effective, showing a response rate of 5% to 7%, and a median PFS of 5-6 months. Patients with a PDGFRA D842V mutation (5-6% of patients with advanced GIST) are generally insensitive to imatinib and the TKI avapritinib has recently been approved (positive opinion CHMP July 2020) for this specific indication, based on a phase 1 SAT (MC Heinrich, 2020).

Activation loop mutations accumulate with increasing frequency after second-line therapy (sunitinib), which also has inadequate activity on activation loop mutant proteins (Heinrich et al, 2008; Liegl et al,

2008). When patients reach 4th line therapy, multiple resistance mutations are present, and presently no other agents have any proven clinical activity.

In May 2020, the US FDA approved Qinlock™ (ripretinib) for the treatment of adult patients with advanced GIST who have received prior treatment with 3 or more kinase inhibitors, including imatinib. There are still no approved treatment options in the EU for this late line (4th line and later line) setting for the GIST patient population.

Unmet Medical Need

Metastatic and/or unresectable GIST that progresses after treatment with 2 currently approved tyrosine kinase inhibitors, imatinib and sunitinib, is a highly incapacitating and life-threatening condition, with poor prognosis (EMA/CHMP/348464/2014). Currently, only regorafenib is approved in the 3rd line setting in Europe, and there are no standard treatment options for this patient population in later line settings in Europe.

Over 95% of GISTs express KIT receptor tyrosine kinase and the majority of GISTs are driven by activating mutations in KIT or the related PDGFRA receptor tyrosine kinase (Liegl, 2008; Heinrich, 2003b). The three available KIT-targeted therapies approved for the treatment of GIST in Europe provide benefits to some patients. However, clinical response is limited and short-lived, and primary resistance to these treatments can also occur for example, primary resistance to imatinib is seen in ~15% of patients (Demetri, 2013).

Resistance to therapy occurs in the majority of patients within a few months to years (Blay,2011), similar to patterns observed in other cancers successfully treated with targeted therapies.

Secondary resistance mutations in KIT after targeted therapy usually arise in the catalytic domain of the kinase. Secondary mutations in KIT typically occur in exons 13 and 14 (near the ATP-binding pocket and the conformation-controlling switch pocket); mutations in this region sterically disrupt drug binding or conformationally activate KIT. Secondary mutations may also occur in the activation loop (conformation-controlling switch) encoded by exons 17 and 18. Activation loop mutations act by shifting the kinase into an activated conformation that is less amenable to drug binding by any of the approved therapies (Gajiwala, 2009).

Third line treatment with regorafenib provides only limited and short-lived benefit, with modest lengthening of PFS by 4.8 months (95% CI 4.0, 5.7) and no improvement of OS and/or QoL compared with placebo. (EMA/CHMP/348464/2014). In the 4th line setting or after, once patients have received imatinib, sunitinib, and regorafenib and experienced disease progression or cannot tolerate regorafenib despite dose reductions, there is no approved treatment option (except for PDGFRA D842V mutations) for patients with advanced or unresectable GIST (Casali, 2018).

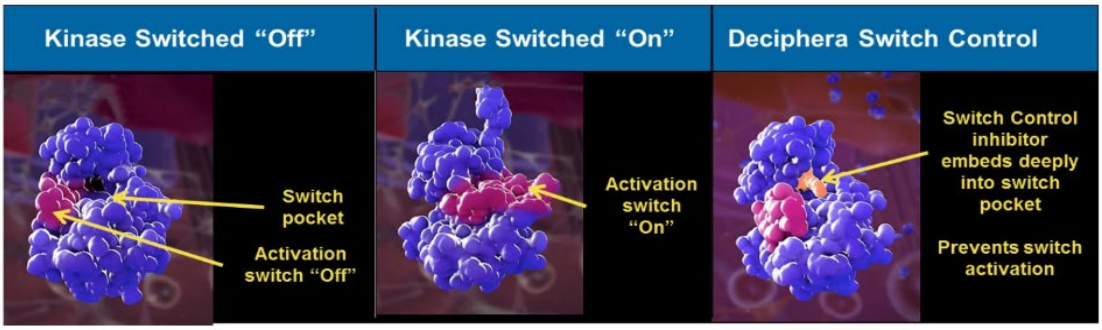
For patients who have progressed on the approved drugs, progression of KIT-driven tumours is primarily based on development of further KIT resistant mutations. At present, there are no approved targeted therapies that broadly inhibit secondary drug-resistant mutations in GIST.

Thus, in Europe, a high unmet medical need remains for kinase inhibitors that are effective against these mutant forms of KIT and PDGFRA.

About the product

Ripretinib is a novel agent belonging to the class of tyrosine kinase inhibitors. The drug product is presented as immediate release white to off-white oval tablets for oral administration. Each tablet contains 50 mg of ripretinib. The recommended dose for clinical use is 150 mg (3 × 50 mg tablets) once daily taken with or without food.

Ripretinib is a switch-control TKI that broadly inhibits KIT and PDGFRA kinase signaling through a dual mechanism of action. Ripretinib is designed to precisely and durably bind to both the switch pocket and the activation loop to lock the kinase in the inactive state, preventing downstream signalling, cell proliferation and to slow down the growth of the tumours and reduce symptoms of the disease. This dual mechanism of action is suggested to provide a broad inhibition of KIT and PDGFRA kinase activity, including wild type as well as primary and secondary mutations. Based on early data, ripretinib also showed inhibition of other kinases in vitro, such as platelet-derived growth factor receptor beta (PDGFRB), tyrosine-protein kinase receptor Tie-2 (TIE2), VEGFR2 and BRAF.



Abbreviation: PDGFRA=platelet-derived growth factor receptor alpha. Kinases have embedded switching mechanisms that conformationally regulate activity. (Left Panel) Inactive form of KIT. Note that the activation switch has not engaged the switch pocket. (Middle panel) Active form of KIT. Note that the activation switch has now moved to engage the switch pocket. (Right panel) Ripretinib binds into key regions of the switch pocket, directly blocking access by mutant exon activation loop switches.

The indication approved by the CHMP is: treatment of adult patients with advanced gastrointestinal stromal tumour (GIST) who have received prior treatment with three or more kinase inhibitors, including imatinib.

Type of Application and aspects on development

The clinical development programme for ripretinib began in 2015 and consists of 8 clinical studies

Three studies have been initiated with ripretinib in patients with GIST: the Phase 1 study (DCC-2618 01-001) in patients with solid tumours including a large proportion of patients with GIST, receiving ripretinib 150 mg QD as either 2nd line (N=31), 3rd line (N=28) or ≥4th line (N=83) treatment; the Phase 3 INVICTUS study in patients with GIST who received ripretinib or placebo for ≥4th line (the pivotal study in this application); and the Phase 3 INTRIGUE study evaluating ripretinib versus sunitinib in 2nd line (all ongoing). Study DCC-2618 01-001 also includes a serial PK cohort of up to 10 patients with GIST and other solid tumours with renal impairment (creatinine clearance (CrCL)) 20 to 50 mL/min, not requiring dialysis), and is currently underway.

Four studies (2 completed, 2 ongoing) are included in this MAA. Two Phase 1 clinical pharmacology studies in healthy adult subjects have been completed and are submitted with this application. Two ongoing studies in patients with GIST form the primary basis for the evaluation of efficacy, safety, and PK for this submission (DCC-2618 01-001 and INVICTUS) with an initial cut-off date of 01 Mar 2019 and 31 May 2019, respectively. An additional safety update to the data cut-off date of 31 Aug 2019 (90-day) was performed for these 2 studies only, appended the present CSR. Furthermore, an additional efficacy and safety update with a data cut-off date of 10 Aug 2020 was performed for these 2 studies; the final data from this data-cut off date is provided in the SmPC.

Scientific advice from the CHMP, SAWP, has been sought related to both preclinical and clinical development of ripretinib, Feb. 2018 (EMEA/H/SA/3764/1/2018/PA/III), however, the clinical questions focused on the INTRIGUE study (DCC 2618 03 002), a single pivotal Phase 3 study in patients with second-line GIST (ongoing), not presented here. Furthermore, in Jan 2020, scientific advice was sought (EMEA/H/SA/3764/2/2020/PA/III), which concerned quality development, pre-clinical development and clinical development. The only clinical question in this advice, however, concerned pharmacodynamic and pharmacokinetic considerations.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as tablets containing 50 mg of ripretinib as active substance.

Other ingredients are: crospovidone (E1202), hypromellose acetate succinate, lactose monohydrate, magnesium stearate (E470b), microcrystalline cellulose (E460) and colloidal hydrated silica (E551).

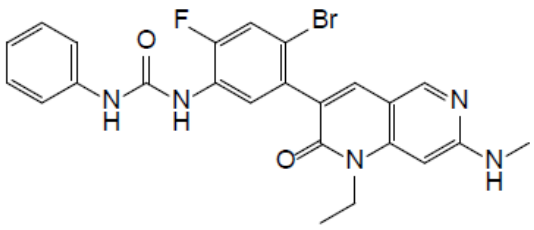
The product is available in white high-density polyethylene (HDPE) bottle with an aluminium foil/polyethylene (PE) tamper evident seal and a white polypropylene (PP) child-resistant closure, together with one PE desiccant canister containing silica gel. Each bottle contains 30 or 90 tablets.

2.2.2. Active substance

General information

The chemical name of ripretinib is 1-(4-Bromo-5-[1-ethyl-7-(methylamino)-2-oxo-1,2-dihydro-1,6-naphthyridin-3-yl]-2-fluorophenyl)-3-phenylurea corresponding to the molecular formula $C_{24}H_{21}BrFN_5O_2$. It has a relative molecular mass of 510.36 and the following structure:

Figure 1: Ripretinib structure



The chemical structure of ripretinib was elucidated by a combination of nuclear magnetic resonance spectroscopy (NMR) and mass spectrometry with confirmatory data from elemental analysis, Fourier transform infrared spectroscopy and ultraviolet spectroscopy. The solid state properties of the active substance were measured by polymorph screening, dynamic vapor sorption, thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), and solid form confirmation.

The active substance is a white to off-white solid crystalline, an anhydrous, unsolvated crystal form. Ripretinib is practically insoluble in aqueous media at physiologic pH values, even in the presence of up to 2% of bile salts. A designation of BCS class 2 or 4 could be assigned based on the measured aqueous solubility combined with the available data on permeability and oral bioavailability in preclinical studies.

Ripretinib has a non - chiral molecular structure. Polymorphism has been observed for ripretinib. A comprehensive and extensive polymorph screen was performed. Upon review of the potential forms identified, it was concluded that only a particular polymorph was relevant to the ripretinib manufacturing process. The selected polymorph is the more thermodynamically stable anhydrous form and was selected as the active substance form for the product. The presence of the desired polymorph is ensured through the manufacturing method of the active substance and controlled in the active substance release specification.

Manufacture, characterisation and process controls

Ripretinib is synthesized in three main stages using commercially available well-defined starting materials with acceptable specifications. One active substance manufacturer is proposed.

The 3 synthetic stages of the manufacturing process are further divided into discrete "steps" equivalent to the unit operations. A high-level flow diagram for these individual steps and in-process controls (IPC) with acceptance criteria are adequately presented in the dossier.

Conversion of starting materials into ripretinib active substance involves 3 chemical transformations and at least 5 crystallisations to generate the active substance. The reaction steps and isolations between starting materials and the final active substance have demonstrated adequate purging and control of impurities as shown by the available batch history data for ripretinib.

Adequate IPCs are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.
Potential and actual impurities were well discussed with regards to their origin, fate, purge and characterisation. Any impurity found above 0.1% in the active substance, in any intermediate or in the starting materials has been identified, isolated/synthesised and fully characterised.

Five impurities are included in the proposed specification as specified identified impurities and nine additional potential impurities are identified and limited as unspecified identified impurities at the qualification threshold (0.15%); the proposed control strategy for each of them takes into consideration their origin and the material attributes and/process parameters that impact their presence. A summary of the toxicological qualification of the related substances limited at levels above the qualification threshold is provided; it is concluded that those impurities are considered qualified at the proposed specification limits in the active substance (see non-clinical section). Although ICH M7 does not apply to this medicinal product because of its indication, an evaluation of the potential

genotoxic impurities has been provided and demonstrates that all specified impurities are Class 4 and designated as non-mutagenic.

Residual solvents are controlled in the release specifications with limits according to ICH Q3C guideline. All the solvents used in the synthesis of the starting materials are controlled in the specifications of the respective starting material. The control strategy for the potential presence of benzene as contaminant in solvents used in the synthesis of the starting materials has been described. Benzene is controlled in the solvents and starting materials specifications, as required.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program using a combination of conventional univariate studies and elements of Quality by Design (QbD), such as risk assessment and design of experiment (DoE) studies. A comprehensive tabular presentation of active substance critical quality attributes (CQAs) and the corresponding control strategy elements is provided in the dossier. No design space is claimed across the entire manufacturing process.

Each step was subject to a risk assessment, that revealed several potential critical process parameters. Based on these studies, proven acceptable ranges (PARs) have been defined for several steps of the manufacturing process of the active substance. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs identified in each stage.

Changes introduced during development have been presented in sufficient detail and have been justified. A single route of synthesis has been used for the production of all nonclinical, clinical, stability, and (pre)-validation and validation batches. This route has been optimised during development resulting in the current intended commercial manufacturing process. Process development optimizations include changes to the synthesis of starting materials (SMs), reagents, and solvents and revisions to process parameters settings allowing for improvements in yield, manufacturability, and control of relevant CQAs. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance is packaged in double linear LDPE bags which complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for: description (visual), identity (FTIR (ATR) - Ph. Eur.), assay, related substances (RP-UPLC), residual solvents ((HS-GC) Ph. Eur. 5.4), sulphated ash (residue on ignition – gravimetric method - Ph. Eur.), solid form confirmation (XRPD), water content (Karl Fischer, Ph. Eur.), particle size (laser diffraction - Ph. Eur.) and elemental impurities (ICP-MS, Ph. Eur.).

The active substance specifications are based on the active substance CQAs. The specification limits for the active substance are based on batch analyses of 3 batches of ripretinib active substance prepared by the commercial process, and batches used for clinical and toxicological studies, taking in consideration also the stability data.

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

Based on the historical microbial enumeration data, coupled with the water activity data, microbial enumeration testing has not been included in the release specification, in line with ICH Q6A, Decision Tree #6.

The control strategy for residual solvents has been detailed in the characterisation of the active substance section.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data for three commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from three primary registration batches of active substance from the proposed manufacturer stored in the intended commercial package in a container closure system representative of that intended for the market for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The parameters tested are the same as for release, with the addition of microbial enumeration. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications under long term and accelerated conditions.

Photostability testing following the ICH guideline Q1B was performed on one batch. No significant differences between the exposed and controlled samples for any of the parameters studied (appearance, assay and impurities) were observed; the active substance is considered photostable. Results on stress conditions were also provided on one batch exposed either as solid or as a solution/suspension preparation to light, heat, acid, base, and hydrogen peroxide. Significant degradation was achieved in acidic conditions, whilst a small increase in degradation products was observed under hydrogen peroxide and in basic conditions.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months in the proposed container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

Ripretinib tablets are white to off-white, approximately 9 × 17 mm, oval shaped tablets, debossed with ‘DC1' on one side. The product is presented as white uncoated tablets of a single strength (50 mg). No overages are proposed. The qualitative and quantitative composition of the finished product is included in the dossier.

Due to the low solubility of ripretinib active substance at physiologic pH and the low to moderate permeability, a finished product manufacturing process that enhanced the solubility and bioavailability of the micronised active substance was investigated during product development. This led to the

development of a ripretinib finished product that incorporates the amorphous active substance in the form of a spray-dried intermediate (SDI). The SDI is subsequently blended with the remaining excipients, granulated through a roller compaction process, and compressed into the tablet.

The quality target product profile (QTPP) for ripretinib tablets was defined as 50 mg immediate release tablets for once daily administration. Key elements of the QTPP are provided in Table 4.

Table 1: Ripretinib finished product quality target product profile

Product Attribute	Target Profile
Route of Administration	Oral
Dose Strength	150 mg daily
Dosage Form	50-mg immediate release tablet
Dosing Regimen	Three 50-mg ripretinib tablets once daily
Product Shelf Life and Storage Conditions	At least 24 months without any special temperature storage conditions
Requirements to Assure Patient Safety and Efficacy at Release and during Shelf Life	• Assay remains NLT 95% of label claim at release and NLT 90% label claim during shelf-life • Limits for degradation product established in accordance with ICH Guidance for Industry • Uniformity of dosage units meets pharmacopeial limits • *In vitro* dissolution profile is indicative of immediate release product • Microbial limits are controlled in accordance to ICH Guidance Q6A • Water content is at acceptable levels as to not have a significant impact on other CQAs
Container Closure System	• Container closure system is sufficiently protective to assure product quality throughout the shelf life • Bottles are capped with child-resistant closures

CQA: critical quality attributes; ICH: International Conference on Harmonisation; NLT: not less than

CQAs for both the SDI and the tablets have been identified. The formulation development consisted of two main parts:

1. development of the spray-dried intermediate, focusing on the assessment of the feasibility of producing an amorphous spray-dried intermediate, including identification of a suitable polymer, solvents, and drug loading;

2. development of the tablet formulation, including identification of the optimum tablet excipients to convert the spray-dried intermediate into tablets that meet the ripretinib finished product CQAs and QTPP.

The excipients selection has been adequately described, the function of the excipients, as well as the critical attributes that can influence the performance of the finished product, are detailed. Compatibility has been investigated through binary blends of the SDI and the excipients; no incompatibilities have been observed. No evidence of phase separation or crystallisation during manufacture or storage of ripretinib tablets has been observed. All excipients are well known pharmaceutical ingredients and their

quality is compliant with the Ph. Eur. with the exception of hypromellose acetate succinate (HPMCAS), a non-phthalate-containing, cellulosic-based polymer, which is described in NF and is commonly used in the manufacture of spray-dried dispersions. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The manufacturing process consists of two main stages: SDI preparation and tablet preparation (dry granulation and compression). The manufacturing process development has been evaluated through the use of risk assessment and DoE to identify the critical process parameters (CPPs). A risk analysis was performed using the failure mode effect analysis (FMEA) method in order to define critical process steps and process parameters that may have an influence on the finished product quality attributes. Identified risks were mitigated by targeted studies, equipment design, batch record instructions and IPCs. The CPPs have been adequately identified. No design spaces are claimed for the manufacturing process of the finished product.

A comprehensive tabular presentation of finished product CQAs and the corresponding control strategy elements is provided in the dossier.
Each stage was subject to a risk assessment, that revealed several potential CPPs. Based on these studies, PARs have been defined for several steps of the manufacturing process of the finished product. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs identified in each stage. During the procedure the applicant has confirmed that for each process step, only one process parameter at a time can be deliberately changed within its PAR while maintaining all other process parameters at their intended target or NOR, in line with ICH Q8 definition.

The quality control (QC) dissolution method employs apparatus 2 (paddles) The speed of the paddle apparatus and the composition of the dissolution media have been adequately investigated and are considered justified. The discriminating ability of the dissolution method was demonstrated by manufacturing products with meaningful variations of the most relevant critical attributes found to impact *in vitro* release rate (e.g. crystallinity, disintegrant level, granule tensile strength, tablet compression force).

Differences between the formulation used for clinical studies and the intended commercial formulation have been adequately justified. The two formulations are considered equivalent. The manufacturing site of the finished product has not changed throughout development. Only minor changes have been made to the commercial manufacturing process compared to that used for the clinical batches.

A comparison of the *in vitro* dissolution profiles of clinical batches and the commercial registration batches using a model independent approach was performed. Bases on the f2 values, in vitro similarity can be concluded for only two clinical batches when compared to the mean of the registration batches, BE study DCC-2618-01-002 (described in the clinical section of this report) supports that the clinical and commercial formulations can be considered bioequivalent based on the criteria presented in EMA's "Guideline on the Investigation of Bioequivalence" CPMP/EWP/QWP/1401/98 Rev. 1/ Corr. These results further demonstrate the discriminatory capability of dissolution method and indicate that, in terms of clinical relevance, the method might be overly discriminating in terms of bioequivalence.

Bulk tablets are stored in double low-density polyethylene (LDPE) bags, sealed with plastic ties. Silica gel desiccant is placed between the bags. The bags are put in a sealed aluminium bag which is placed in a HDPE drum. The commercial packaging consists of a primary packaging which is a white HDPE bottle with an aluminium foil/PE tamper evident seal and a white PP child-resistant closure, together with one PE desiccant canister containing silica gel.

The contact materials of the bulk and commercial packaging comply with Ph.Eur. and EC requirements. The child-resistant closure is in compliance with ISO 8317:2015.

The choice of the container closure systems has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

As indicated above, the manufacturing process consists of 2 main stages: manufacture of the SDI and manufacture of the tablet.

In stage 1, ripretinib active substance is mixed with HPMCAS to produce an amorphous SDI.

In stage 2, the SDI is combined with microcrystalline cellulose, lactose monohydrate, crospovidone, silica colloidal hydrated, and magnesium stearate. The combined components are granulated using a roller compaction process and then blended with extragranular silica colloidal hydrated and magnesium stearate. The final blend is compressed into tablets containing 50 mg of ripretinib.

A flow diagram for the finished product manufacturing process is provided in the dossier.

Critical process parameters, including their proven acceptable ranges, targets and/or normal operating ranges as discussed previously were justified. The in-process controls are adequate for this type of manufacturing process.

The spray-drying step is considered to be a non-standard manufacturing step. The SDI manufacturing process have been validated by manufacturing three consecutive batches of the SDI intermediate. A satisfactory validation protocol has been submitted. Through the batch data provided, it has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release specification, includes appropriate tests for this kind of dosage form: description (visual inspection), identification (HPLC-UV), assay (HPLC-UV), degradation products (HPLC-UV), uniformity of dosage units (HPLC-UV /Ph. Eur.), dissolution (HPLC-UV /Ph. Eur.), water content (Karl Fischer - Ph. Eur), solid form XRPD (Ph. Eur.) and microbial limits (Ph. Eur.).

The proposed specification tests are in line with ICHQ6A and Ph. Eur. requirements and suitable for an immediate release tablet. The limit for water content has been justified based on historical batch data at release, the maximum level observed during stability, and taking into consideration process and analytical variability.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for nine clinical batches and six commercial full-scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released to the market based on the above release specifications, through traditional final product release testing.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Stability of the product

Stability data from 3 commercial scale batches of finished product of each pack size (bottles with 30 and 90 tablets), obtained from three bulk tablets batches, stored for up to 24 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of ripretinib finished product are identical to those proposed for marketing and were packed in the packaging proposed for marketing.

Samples were tested for the shelf life specification which includes tests for: assay, specified, unspecified and total degradation products, dissolution, water content, solid form, and microbial quality. No significant changes can be observed and the only clear trend is the increase of the primary degradation product in the accelerated study. However, at six months, the limit is still within specification. The assay limit for the shelf-life specification was tightened during the procedure.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. In the light exposed open container, the tablets failed specification. Test conditions evaluating the closed container (both exposed and protected) exhibit passing results for all test attributes. These results confirm the suitability of the intended commercial primary package.

Samples of the finished product were subjected to stress conditions (acid, base, oxidation, heat, heat and moisture combined, and exposure to light). Out of specification results were obtained after exposure to light. The analytical procedures used are stability indicating.

A bulk stability study has been conducted on two bulk tablet batches stored for up to 6 months at 20 °C to 25 °C in the proposed bulk container closure system. The data supports a maximum storage of 6 months (excursions permitted between 15°C to 30°C) for the bulk tablets before packaging in the final primary container for marketing.

An in-use stability study, simulating the in-use conditions and stored at under long term conditions (2ºC / 60% RH) for up to 30 days has been conducted on two primary batches packed in both pack sizes (bottles for 30 and 90 tablets). Samples were tested for description, assay, degradation products, dissolution and solid form, according to shelf-life specifications and analytical procedures; the data supports the 30 day in-use period when the product is stored according to the label. No in-use period restriction is therefore proposed.

Based on available stability data, the proposed shelf-life of 36 months and storage conditions "Store in the original package and keep bottle tightly closed in order to protect from light and moisture" as stated in the SmPC (section 6.3 and 6.4) are acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products. No other raw materials of human or animal origin are used in the manufacture of ripretinib active substance or finished product. Magnesium stearate is of vegetable origin.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. Due to the low solubility of ripretinib a SDI that incorporates an amorphous form of the active substance and enhances its bioavailability was developed.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the active substance and finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non clinical aspects

2.3.1. Pharmacology

Ripretinib is a novel, oral inhibitor of KIT kinase, developed by Deciphera, using its proprietary kinase switch control inhibitor technology platform. The objective of the program was to develop a substance binding to a broad range of constitutively active KIT mutant kinase forms and induce them to adopt inactive conformations.

Primary pharmodynamics

Ripretinib and the active metabolite DP-5439 were shown to be potent inhibitors of KIT and PDGFRA kinases *in vitro*. Ripretinib and DP-5439 demonstrated inhibition of these kinases in both recombinant enzyme and cell-based assays. In a study with a large number of clinically relevant KIT mutants, the inhibitory activity of ripretinib and DP-5439 was compared to the approved KIT inhibitors imatinib, sunitinib and regorafenib.

IC_{50} values for ripretinib and DP-5439 inhibition of a large panel of KIT mutants at 10 μM ATP

Kinase	Exon mutation(s)	Ripretinib	DP-5439	Imatinib	Sunitinib	Regorafenib
		IC_{50} (nM)				
KIT wild type	-	16	7.0	114	12	201
KIT del557-558	11	0.08	0.06	0.99	0.67	4.5
KIT V559A	11	0.09	0.08	2.0	0.59	6.9
KIT V559D	11	0.17	0.11	26	121	29
KIT V560G	11	0.53	0.13	23	120	11
KIT K642E	13	1.2	0.75	15	1.0	57
KIT V654A	13	39	42	> 1000	0.48	389
KIT T670I	14	3.6	1.1	> 1000	0.99	20
KIT D816E	17	0.27	0.17	84	39	87
KIT D816F	17	0.29	0.21	> 1000	251	> 1000
KIT D816H	17	0.34	0.22	> 1000	80	494
KIT D816I	17	0.26	0.17	> 1000	160	> 1000
KIT D816V	17	0.25	0.16	> 1000	113	> 1000
KIT D816Y	17	0.42	0.26	> 1000	82	> 1000
KIT D820E	17	0.20	0.13	8.9	13	20
KIT D820Y	17	0.15	0.11	23	7.4	15
KIT Y823D	17	0.14	0.10	76	6.8	5.5
KIT V560G/D816V	11/17	0.12	0.09	> 1000	102	> 1000
KIT V560G/N822K	11/17	0.15	0.11	370	104	90

Ripretinib and DP-5439 blocked cellular proliferation or KIT/PDGFRA phosphorylation of GIST, AML, and mastocytosis cell lines driven by KIT mutations, induced apoptosis in KIT mutant mast cells and prevented the emergence of drug resistance in KIT mutant cellular saturation mutagenesis assays. In cellular assays, ripretinib and DP-5439 also inhibited several key kinases that play important roles in the tumour microenvironment, including vascular endothelial growth factor receptor 2 (VEGFR2), colony stimulating factor 1 receptor (CSF-1R), PDGFRB, and tunica interna endothelial kinase 2 (TIE2).

In vivo, ripretinib inhibited mutant KIT phosphorylation and signaling in PK/PD xenograft models. *In vivo* inhibition of KIT was associated with inhibition of tumour growth in a variety of tumour xenograft models including exon 11 mutant KIT GIST T1 xenografts and an imatinib-resistant exon 17 mutant KIT GIST patient-derived xenograft. Ripretinib treatment also led to complete tumour regression in the H1703 PDGFRA-amplified lung cancer xenograft model. Ripretinib treatment was well tolerated in mouse studies, with a maximum tolerated dose ≥180 mg/kg twice daily.

Secondary pharmacodynamics

In a large panel of 295 human kinase activity assays, ripretinib was found to inhibit 19 kinases within 10-fold of its half-maximal inhibitory concentration (IC50) value for KIT inhibition, inclusive of primary targets VEGFR2 (KDR), PDGFRA/B, and CSF-1R (FMS). Ripretinib showed > 10-fold specificity versus 273 other kinases and > 50-fold specificity versus 256 of the kinases in the panel. Many kinases identified to be inhibited within 10-fold of KIT in the large panel study utilizing a low 10 μM adenosine triphosphate (ATP) concentration were found to be much less inhibited when evaluated at relevant cellular levels of ATP (4 mM). Cellular studies revealed that ripretinib functionally inhibited kinases including TIE2, CSF-1R, PDGFRA/B, and VEGFR2, but showed weak activity for cellular RAF kinases.

Ripretinib was also evaluated versus a battery of 135 receptors, ion channels, and enzymes. Screening at a concentration of 10 µM did not identify any significant liabilities that precluded development.

Safety pharmacology

Ripretinib showed no CNS or respiratory effects when administered orally to Sprague-Dawley rats at 15, 60 or 300 mg/kg. he approximate maximum plasma drug concentration (C_{max}) in these studies was expected to be 3460 ng/mL and the expected area under the plasma concentration-time curve (AUC) from time 0 to 24 hours (AUC_{0-24}) was 36300 ng·h/mL at 300 mg/kg based on Day 1 toxicokinetic results from the 4-week toxicity study in male rats.

For CV assessment, the Predictor™ hERG Fluorescence Polarization Assay by Invitrogen was used to assess hERG channel binding potential in a homogenous, fluorescence polarization-based format. The average hERG IC_{50}/concentration required to achieve 20% inhibition (IC_{20}) values were 7.9 µM/2.0 µM for ripretinib and 2.5 µM/0.41 µM for DP-5439.

Ripretinib had no effect on CNS and respiratory systems. Single doses of ripretinib resulted in increased diastolic pressure and mean arterial pressure in a CV safety study. There were no changes to systolic pressures or arterial pulse pressure. Increases in HR and lower QT and PR interval (likely secondary to changes in HR) were observed, but there was no change in QTc values. The magnitudes of the blood pressure and HR changes were considered noteworthy, but do not represent a severe toxicity. *In vitro*, ripretinib and metabolite DP-5439 exhibited weak binding to hERG channel components.

The telemetry dog study showed ripretinib-related CV changes with a 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. QTc values were not significantly increased with ripretinib treatment. HRs remained elevated at the end of the telemetry collection (19 hours post dose), but differences were slightly less suggesting that HRs were beginning to recover at 19 hours post dose. Animals given 7, 20, and 75 mg/kg had plasma concentrations (mean ± standard deviation) of 212 ± 80, 284 ± 131, and 586 ± 222 ng/mL, respectively.

2.3.2. Pharmacokinetics

Quantitative high-performance liquid chromatography (HPLC)-tandem mass spectrometry (MS/MS) bioanalytical methods were developed and fully validated in rat and dog plasma. These assays were used to support the GLP toxicokinetic studies in the rat and dog.

Absorption

The PK of ripretinib was assessed after a single IV bolus dose or oral doses in mice, rats, dogs, and cynomolgus monkeys. A multidose oral PK study was performed in dogs. In rats, the unformulated mesylate salt of ripretinib (DP-4851.M) exhibited 28% bioavailability, an IV elimination half-life of 2.0 hours, and an IV clearance rate (Cl_obs) of 0.64 L/h/kg. The volume of distribution (Vz_obs) was 1.87 L/kg. In dogs, ripretinib (DP-4851.M) exhibited 24% bioavailability, an IV elimination half-life of 2.72 hours, a low Cl_obs of 0.27 L/h/kg, and a Vz_obs of 1.03 L/kg.

Distribution

The plasma protein binding of ripretinib was investigated in mouse, rat, dog, cynomolgus monkey, and human plasma. Percent bound values were approximately 99.9% in all species. Ripretinib was moderately bound to blood cell components, but primarily partitioned to plasma.

Quantitative whole-body autoradiography tissue distribution of [^{14}C] -ripretinib (~100 µCi/kg) was assessed in SD rats and pigmented Long Evans (LE) rats. Radiolabel associated with [^{14}C]-ripretinib was extensively bound to melanin-containing tissues in pigmented LE rats such as eye ciliary body, eye uveal tract, and eyes, and the radiolabel binding showed a long half-life. In non-pigmented 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.

In an *in vivo* distribution study, SD rats were assessed for the uptake of ripretinib into the brain following a 0.9 mg/kg IV dose. Plasma and brain samples taken over 24-hour time points post dose show presence of ripretinib and its metabolite DP-5439 in plasma at levels similar to those observed in previous IV dose studies. Analysis of brain samples demonstrated that ripretinib exposures for C_{max} and AUC were 3.6% and 2.2% respectively, relative to the levels in plasma. No measurable levels of metabolite DP-5439 were present in the brain tissue.

Metabolism

The overall extent of ripretinib metabolism by hepatocytes from highest to lowest followed the rank order monkey > dog > rat > mouse ≈ human. The metabolic pathways of ripretinib were qualitatively similar across all five species and resulting in no human-specific or human-disproportionate metabolites.

In vivo metabolism studies conducted with [^{14}C]-radiolabeled ripretinib in SD rats and in beagle dogs show the presence of same ripretinib metabolites at similar plasma concentrations relative to *in vitro* studies. In a rat mass balance study, pooled composite plasma samples from SD rats profiled contained nine radioactive components. Unchanged ripretinib was the major circulating component in male and female rats and accounted for approximately 51% and 71% of the total radioactivity exposure, respectively. *N*-desmethylated metabolite DP-5439 (M5) was the major circulating metabolite and accounted for approximately 38% and 22% of the total radioactivity exposure in males and females, respectively. Similarly, in the dog mass balance study, pooled composite plasma samples profiled contained four radioactive components. Of the total radioactivity in the sample, unchanged ripretinib represented approximately 69% and DP-5439 represented approximately 22% in both males and females.

2.3.3. Toxicology

The non-clinical toxicology profile of ripretinib (DCC 2618) has been evaluated in rats, rabbits, and dogs in agreement with relevant guidelines.

The oral route of administration was utilized in all pivotal toxicology studies to match the intended clinical administration route.

The treatment with ripretinib should continue as long as benefit is observed or until unacceptable toxicity. In accordance with the ICH S9 guideline for anticancer pharmaceutical for patients with advanced cancer, nonclinical studies of 3 months duration are considered sufficient to support marketing. The pivotal studies were conducted in compliance with GLP.

In the ripretinib toxicology program, rats and dogs were selected as the primary test species for general toxicity studies.

Single dose toxicity

No single-dose toxicity studies have been performed. This is acceptable.

Repeat-dose toxicity

Ripretinib was evaluated in repeat dose toxicity studies in rats and dogs (14 days, 4 weeks with 4 weeks recovery, 13 weeks with 4 weeks recovery).

The most pronounced effects were inflammatory responses correlating with skin changes, elevated hepatic enzyme activity and gastrointestinal effects.

Morbidity and mortality

Ripretinib was not tolerated in rats and dogs at high doses. In rats, the highest tested dose, 300 mg/kg/day, was tolerated in the short-term studies. In the 3-months study however, three animals administered 300 mg/kg were sacrificed in moribund condition on day 22 and 29 of treatment. The animals had discoloured skin, scabs on the tail and/or feet, scaly skin on the tail and thinning of the hair coat. One of the animals was also evaluated microscopically and was observed with marked haemorrhage and neutrophilic inflammation of the urinary bladder with likely extension into the kidney. Several of the remaining animals in the 300 mg/kg group was administered NSAID due to the lesions in the skin.

In dogs, in the non-pivotal study 1 (of 2) male was sacrificed after 5 doses of DCC-2618. This animal exhibited repeated emesis which lead to lethargy, dehydration, intermittent tremors and marked decreases in electrolytes. In the 4 weeks study, dosing was suspended on day 8-14 in several animals of the 20 and 75 mg/kg groups. Dose-limiting toxicity effects included severe skin reactions that manifested as red, dry, scaly, and/or flaky skin of the feet, ears, swollen muzzle, periorbital area, inguinal area, and/or ventral thoracic area; ear discharge; and thinning of the hair coat, with microscopic findings of hyperkeratosis. These changes were progressive, were dose-related in severity, and warranted suspension of dosing and/or early termination of animals at 20 and 75 mg/kg/day. In the 13-week study, 1 female in the 10 mg/kg group was sacrificed in a moribund condition on Day 23. It is likely that it was a pre-existing weakened state that was exacerbated by the test article that led to the moribund state.

Body weight & food consumption

Administration with ripretinib was associated with decreased body weight. The decreased body weight was observed also during recovery and were preceded by the lowered food consumption. During the 13-weeks studies animals were supplemented with DietGel (rats in 300 mg/kg) and canned food (individuals in 5 and 10 mg/kg groups).

Skin

Lesions of the skin and related observations were very common and also led to the early sacrifice of animals as discussed above. Furthermore, animals were treated with NSAID, antibiotics and silver sulfadiazine cream for the red and thickened skin, scabs and sores and pruritus.

In the 13 week study in rats discoloured skin, and skin lesions at ≥ 30 mg/kg/day; alopecia or thinning hair coat were noted. These findings correlated with clinical pathology findings indicating an inflammatory and/or a stress response that correlated with skin changes. The histopathological investigation revealed hyperplasia and hyperkeratosis of the skin/subcutis in all dose groups. The observation was only partially reversible.

In the pivotal 4-week study in dogs, ripretinib at doses of 20 and 75 mg/kg resulted in serious skin changes requiring discontinuation of dosing and/or early sacrifice (see section on mortality above). Hyperkeratosis of the skin was observed in the histopathological evaluation.

In the 13-weeks study in dogs, daily administration of 2.5, 5, or 10 mg/kg/day ripretinib resulted in skin lesions and thinning hair coat/hair loss at all doses, and the skin feeling warm to the touch at ≥ 5

mg/kg/day Clinical pathology findings were consistent with an inflammatory and/or stress response. Microscopic findings of hyperplasia/hyperkeratosis in the skin were observed.

Alopecia, palmar plantar erythrodysaesthesia syndrome, and dry skin are listed as very common adverse drug reactions in patients. Pruritus, dermatitis acneiform, hyperkeratosis, and rash maculopapula as common. The exact mechanism behind the findings in the skin is not understood. However, since skin disorders are commonly observed in patients, and also easily monitored, the mechanism is not considered crucial for safety assessment of ripretinib. Nevertheless, as discussed above, the applicant is asked to further discuss the skin findings in relation to the acute toxicity that lead to the preterm sacrifice of several animals.

Lymphoid tissues and immune system

The increased number of leukocytes (WBC, NEU, MON, EOS, Large unstained cell, BAS) and PLT and higher fibrinogen concentration in the 13-weeks repeat dose study in rats were suggestive of an inflammatory response. This finding correlated with the macroscopic and microscopic findings in the skin. The inflammatory reactions were also seen in the minimally to mildly lower protein and albumin concentrations and albumin:globulin ratio

In the dog studies an increase in white blood cells, platelets, and fibrinogen were also seen. The weight of the thymus was reduced which correlated with the decreased number of lymphocytes observed microscopically. No effect on thymus was not observed in the 13-week study.

Hematology

In rats treated with ripretinib, lower red cell mass (RBC, HGB, HCT) was accompanied by a regenerative response, as supported by the higher reticulocyte count and changes to red blood cell indices (MCV, MHC, RBC width). These red blood findings did not have clinical or microscopic correlates and were of unclear mechanism.

Cardiovascular

In the 14 day dose-range finding study in rats, potentially ripretinib related microscopic heart changes were identified. In the longer GLP-compliant studies no cardiac injury was observed.

In the 13-week study in rats, ripretinib-related minimal to moderate hypertrophy/hyperplasia of blood vessels occurred in the liver, lungs, and/or mesenteric lymph node of dosing phase animals administered ≥ 100 mg/kg/day. Hypertrophy/hyperplasia of vessels generally decreased in incidence and/or severity in recovery sacrifice animals administered ≥ 100 mg/kg/day, which suggested partial reversibility.

Liver

In rats exposed to ripretinib for 13 weeks, increased hepatic enzyme activities (ALT and/or ALP) was observed. These findings correlated with changes in the portal vasculature in the liver. The hypertrophy/hyperplasia of the vessels was most pronounced in male rats.

In the 4-weeks study in the dog, ALT was reduced. The liver weight was however increased in male animals administered 75 mg/kg and in one female animal in the 20 mg/kg group. The increased weight correlated with cytoplasmic rarefaction of hepatocytes. In the 13-week study in dogs (with lower doses administered) no observations suggestive of liver toxicity was noted.

Gastrointestinal

In rat diffuse hyperplasia/hyperkeratosis in the non-glandular stomach was noted in both the 4- weeks and 13-weeks studies. This was only partially reversed during the recovery phase. In the longer study, hyperplasia/hyperkeratosis was observed also in the skin/subcutis, tongue and esophagus.

The non-glandular stomach of rodents serves as a storage organ and is not present in humans. The clinical relevance of findings in the non glandular stomach could thus be questioned although it is likely that the squamous mucosa lining in the esophagus in species without a forestomach would react similar as the forestomach if the exposure would be equivalent. In the rodent, it is possible that the exposure time to the mucosa is prolonged due to residual ripretinib in the forestomach. In the patients, ripretinib is administered in tablets and it is therefore not likely that the mucosa of the human esophagus would be exposed for a prolonged time. No study of the local tolerance of ripretinib has however been conducted.

In the rat, marked degeneration of Brunner's glands in the proximal duodenum was noted.

In dogs, ripretinib common clinical signs were generally indicative of gastrointestinal effects (emesis and/or abnormal feces).

Teeth

Missing or white teeth were observed in the 13-week rat study. During the recovery phase, this observation was noted in animals not previously observed with the findings. The microscopic evaluation showed minimal to marked degeneration of incisor teeth. Loss and/or disorganization of odontogenic cells, changes in dentin. The upper molars were found unaffected. No effects on teeth were observed in the dog studies.

Skeletal

Ripretinib-related increased osteoblastic surface and/or decreased trabeculae of the femur occurred in dosing phase animals administered ≥ 30 mg/kg/day in the 13-weeks rat study. These findings generally decreased in incidence and/or severity in recovery sacrifice animals which suggested partial reversibility. No observations were made in the dog studies.

Reproductive organs

In the 13-week study in rats, increased incidences of mononuclear infiltration and cellular debris occurred in the epididymides and had not resolved by the end of a 4-week recovery period. Tubular atrophy and degeneration of the testes, as well as atrophy of the seminal vesicles, were observed at the end of the 4-week recovery period. Since the recovery period was 28 days and the spermatogenic cycle in rats is approximately 52 days, reversibility might not be expected. The histopathologic findings in male reproductive tissues of rats treated with ripretinib suggest a potential effect on fertility in humans, as seen with other tyrosine kinase inhibitors. No histopathological findings were observed in the female reproductive tissue.

Pulmonary system

In rats, increased absolute and relative lung weights with no correlating microscopic findings was observed in the 4 weeks study. In the longer study, hypertrophy and hyperplasia and/or slight vacuolation of bronchiolar epithelium was observed. No effects on the pulmonary system were observed in the dog studies. The cause of these findings and the clinical relevance is not known. Interestingly, a very common adverse reaction in the patients was dyspnoea. No effects on respiratory parameters were observed in the safety pharmacology study, in which only one dose of ripretinib was administered. Thus, safety pharmacology studies does not reflect the situation after chronic treatment.

Toxicokinetics

Toxicokinetics of ripretinib and its active metabolite DP-5439 were characterized in all the pivotal repeat dose toxicity studies.

Female rats had approximately 2-fold higher exposure than males for ripretinib. The exposure of the metabolite was similar in male and female rats. No sex-dependent difference in exposure was observed in dogs.

Exposures in rats and dogs were in general less than dose proportionate.

Exposures were lower on the last day of the study than on Day 1. There was no evidence of accumulation of ripretinib after multiple dosing of ripretinib in rats.

Exposure margins between the NOAEL and patient exposures were below 1. The same is in general true for margins to exposure at maximal tolerated dose. The rat exposure margins were slightly larger than when comparing exposure in dogs vs patients.

Genotoxicity

A complete package of genotoxicity studies in agreement with the ICH S2 (R1) guideline, including tests for gene mutations in bacteria, chromosomal aberrations in human lymphocytes, micronuclei and comet assay in vivo (rat), has been performed with ripretinib and the metabolite DP-5439.

Both ripretinib and DP-5439 were found negative in the bacterial mutation assay.

Ripretinib, but not DP-5439, was found positive in the in vitro micronucleus assay using human peripheral blood lymphocytes.

In the *in vivo* micronucleus assay, ripretinib did not induce micronuclei in polychromatic erythrocytes of the bone marrow. Furthermore, no DNA strand breaks were observed in the liver in the comet assay.

Systemic exposure and presence of the metabolite were confirmed in the in vivo study. The bone marrow is a well perfused tissue and levels of drug related materials in blood or plasma are generally similar to those observed in bone marrow. The liver is expected to be exposed for drugs with systemic exposure.

The negative results in the in vivo assays are considered sufficient to demonstrate the absence of significant genotoxic risk.

Carcinogenicity

Carcinogenicity studies have not been conducted with ripretinib.

Reproductive and developmental toxicity

A reproductive toxicity program concerning the embryofetal toxicology assessment was performed with ripretinib. The conducted studies included dose-range finding embryo-foetal development studies in rats and rabbits and a pivotal embryo-foetal development study in rats.

The pivotal study is stated to be GLP-compliant. The reproductive toxicity program is in accordance with ICH S9 guideline which states that studies on fertility and early embryonic development, and pre- and postnatal toxicology studies are generally not warranted to support marketing of pharmaceuticals for the treatment of patients with advanced cancer. The study package is thus in general considered adequate and relevant for evaluation of potential risks for humans.

Male and female fertility

No fertility and early embryonic development studies were conducted with ripretinib.

According to ICH S9, a study of fertility and early embryonic development is not warranted to support the marketing of pharmaceuticals for the treatment of patients with advanced cancer. Information

from general toxicity studies on the effect on reproductive organs should be used for the assessment of impairment of fertility.

Embryo-foetal development

Embryo-foetal development was investigated in rats and rabbits. Dose range finding studies were conducted in both species.

In the DRF study in rats, ripretinib was administered at doses up to 300 mg/kg during the period of organogenesis (GD6-17). The two highest doses, 300 and 75 mg/kg, induced total litter loss due to early resorptions. In the highest dose with surviving foetuses (20 mg/kg) external anomalies were observed in the foetuses. The 20 mg/kg dose was selected as the high dose in the pivotal study.

DCC-2618 related developmental toxicity, characterized by malformations and variations, primarily of the cardiovascular and skeletal systems, was observed at 20 mg/kg. Skeletal variations were also observed in the 5 mg/kg group and are considered related to exposure of DCC-2618. The NOAEL proposed by the applicant, 5 mg/kg, was thus not accepted but lowered to 1 mg/kg.

The exposure margins at GD11 at NOAEL (1 mg/kg) vs exposure in humans are 184/9856= 0.02 for DCC-2618. The concentration of the metabolite at this dose was not detectable. Teratogenicity observed as malformations, was observed at 20 mg/kg, with the exposure margins at GD11 of 9410/9856= 1 and 888/8146=0.1 for DCC-2618 and DP-5439 respectively.

A DRF study was also conducted in rabbits. In this study ripretinib was administered at doses up to 150 mg/kg during the period of organogenesis (GD7-19). The highest dose, 150 mg/kg, induced total litter loss due to early resorptions. Embryonic survival was also reduced in the 40 mg/kg group.

In the 40 mg/kg, anomalies were observed in one fetus. The applicant claims that these anomalies are unrelated to administration of ripretinib. This is not agreed upon. It is not possible to exclude that the findings were caused by ripretinib from a dose-range finding study with limited number of treated animals. This claim would need to be supported by a pivotal study showing absence of the findings. As commented above, a pivotal study in rabbits is however not considered warranted.

The exposure margins at GD13 in the lowest dose group (2 mg/kg) in which decreased maternal body weight gain was observed vs exposure in humans are 1640/9856= 0.2 and 88.9/8146=0.01 for DCC-2618 and DP-5439 respectively. Embryonic lethality occurred at 40 mg/kg, with the exposure margins at GD13 of 48900/9856= 5 and 5910/8146=0.7 for DCC-2618 and DP-5439 respectively.

No pre- and postnatal development studies or juvenile animal studies were conducted.

Teratogenicity and developmental toxicity have been reported in rats and/or rabbits with other tyrosine kinase inhibitors. Many of these effects were related to delays in skeletal ossification and occurred at a dose that resulted in reduced fetal body weights and skeletal malformations. These effects are not unexpected given the role of tyrosine kinases in fetal development.

Metabolites

No specific studies with metabolites have been conducted. The exposure of the metabolite DP-5429 was measured in all the pivotal toxicity studies. The data indicates adequate exposure of the metabolite.

Impurities

Three impurities in the drug substance specification are specified above the ICH Q3A Impurities in New Drug Substances qualification threshold of 0.15% and one drug product degradant.

DP-4847 is specified above the International Conference on Harmonisation (ICH) Q3B(R2), *Impurities in New Drug Products.*.

Rat and dog toxicity studies were used to calculate exposure margins. The test material used in the 13 week studies were exposed to accelerated aging (50°C/75% RH, open) for 3-4 weeks. The impurities can be considered adequately qualified at the proposed specification limits.

Phototoxicity

Ripretinib absorbs light within the range of natural sunlight, with a molar extinction coefficient >1000 $M^{-1}cm^{-1}$ between 290 and 700 nm. In other words, ripretinib has a photoreactive potential.

Ripretinib and the active metabolite DP-5439 were investigated in the 3T3 NRU assay. Both substances demonstrated phototoxic potential in the assay.

As described in the section on pharmacokinetics, ripretinib was shown to be highly bound to melanin-containing tissues.

2.3.4. Ecotoxicity/environmental risk assessment

In the screening for persistence, bioaccumulation and toxicity (PBT), the applicant provided a Log P value of 3.69. The value was determined by microemulsion electrokinetic chromatography (MEEKC) using capillary electrophoresis. Since this method is not a preferred method according to the current guideline the applicant should determine the logKow experimentally according to the current ERA guideline. The applicant has agreed to conduct a study to determine the logKow experimentally and states the study report will be submitted in March 2023 (see post authorisation measures section-REC). The log Kow is pending, and thus also the PBT assessment.

The Phase I exposure assessment the Fpen was refined. Using the prevalence data used in the Orphan Designation renders a PECSW that triggers a Phase II assessment (0.012 µg/L). The applicant has however provided an alternative approach in which the action limit for Phase II is not reached. A refined Fpen is presented with worst case scenarios for the GIST patients actually eligible for treatment with ripretinib, taking into consideration that ripretinib is indicated for the treatment of patients with advanced GIST who have received at three or more kinase inhibitors, including imatinib. Also the mean length of the treatment was included in the refinement (36 weeks). This rendered a Fpen refined of 0.00013, which resulted in a PECsurfacewater of 0.0098 µg/L. Nota bene, the mean duration of a treatment period and not the worst case period, was used in this calculation. In discussions with EMA the applicant has received the advice "The argument based on the fact that GIST is in 3rd or 4th line of treatment and that the prevalence of patients concerned would even be lower than the one used in their calculation is a possibility, but the applicant needs to provide published data to demonstrate that."

The applicant's refinement of the Fpen is considered acceptable. The PECSW will thus be below the trigger value for a Phase II assessment. The applicant should note that future variations of the indication is likely to shift the PECSW to reach the action limit for entering Phase II assessment.

Table for the assessment report providing relevant endpoints of the environmental risk assessment of human pharmaceuticals.

Summary of main study results

Substance (INN/Invented Name): Ripretinib
CAS-number (if available):

PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or …	Pending	Potential PBT (Y/N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}		B/not B
	BCF		B/not B
Persistence	DT50 or ready biodegradability		P/not P
Toxicity	NOEC or CMR		T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB The compound is considered as vPvB The compound is considered as PBT		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.0098	µg/L	> 0.01 threshold (N)
Other concerns (e.g. chemical class)			(N)

2.3.5. Discussion on non-clinical aspects

Pharmacology

Ripretinib and the main metabolite Dp-5439 are inhibitors of KIT and PDGFRA kinases with IC50 below 10 nM for the WT kinases. Ripretinib shows activity at a large number of mutant KIT forms, many of which are associated with resistance to the previously approved KIT inhibitors imatinib, sunitinib and regorafenib. In an in vitro model for tolerance development based on chemical mutagenesis and cell culture in presence of ripretinib, no secondary KIT mutations resistant to ripretinib developed. In contrast, on culture with imatinib outgrowth with a number of KIT mutated clones occurred. For both substances there were occurrences of outgrowth with clones which showed no mutations KIT, likely due to activation of other oncogenic pathways. These data could suggest that ripretinib would be less likely to be associated with primary and secondary resistance than the approved KIT inhibitors.

No data are presented on isolated KIT from toxicology species (rat, dog) to allow for a conclusion on the pharmacological relevance of these species. However, among the cell lines tested P815, a mouse cell line with a mutated KIT, showed a similar response as the human cell lines. A sequence comparison shows 94.3% identity between mouse and human in the the KIT kinase domain. For rat and dog the homology to human KIT is 94.8 and 98.6 %, respectively. The differences are located at positions unlikely to influence the activity of ripretinib. Considering the presence of toxicology findings in rat and dog which are likely to be due to on-target effects, it is agreed that rat and dog are pharmacologically relevant species for toxicity evaluation.

In addition to KIT, ripretinib has relevant activity at a number of close related kinases. While some of these kinases were shown to provide anti-tumour activity through their importance for the tumour microenvironment (VEGFR2, PDGFRA, PDGFRB; TIE), these kinases are also of importance for normal tissue function and likely to be of importance for the safety profile.

Ripretinib showed no liability for hERG inhibition in an in vitro study. In the dog cardiovascular safety study, increased heart rate and blood pressure was observed. There were no findings suggesting an

arrhythmic potential. Exposure at the high dose 75 mg/kg was 586 ng/ml. This is about equal to human Cmax (761 ng/ml).

Rat safety pharmacology studies on CNS and respiratory effects did not demonstrate any safety concerns of clinical importance. No TK data were collected in these studies but based on data from the 4-week rat toxicity studies a Cmax of 3460 ng/ml was expected at the high dose of 300 mg/kg.

Pharmacokinetics

Validated methods were established for measurement of ripretinib and the main metabolite DP-5439 in toxicity species.

Absorption was adequately characterised in animals.

The applicant performed dedicated studies to investigate the distribution to the brain in mice and rats. These studies showed minimal distribution of ripretinib and the main metabolite DP-5439 to the brain (<4%). While tumour metastises localizing to the brain may impair the blood-brain barrier, these data suggest ripretinib not be an effective drug in the cases.

In the QWBA study, binding to melanin and retention in tissues such as eye ciliary body, eye uveal tract and eyes was identified. Ripretinib has showed phototoxic potential and this is issue to be considered for the clinical safety evaluation (see Toxicology section).

The metabolism was evaluated in mass balance studies in rats and dogs. In both species, ripretinib was the major circulating form and the pharmacologically active metabolite DP-5439 was the main metabolite with AUC values 40-60% of the parent. DP-5439 is also the only main metabolite identified in humans.

Toxicology

The rat and dog were selected as primary test species for general toxicity studies. The justification for the relevance of these test species includes: in vitro studies of metabolic stability and metabolite identification comparing mouse, rat, dog, monkey, and human, where rat and/or dog were demonstrated to form the same metabolites as humans. While there are no data on primary pharmacology in rats or dogs, strong sequence homology in critical parts of the KIT molecule suggests these animal models to be pharmacologically relevant.

In the repeat dose toxicity studies, high doses of ripretinib were not tolerated and both rats and dogs were sacrificed early. The animals that was sacrificed early suffered from severe lesions and signs of inflammation. The cause of the acute toxicity was however initially only briefly discussed. Upon request the applicant further discussed the acute toxicity and possible mechanisms. Inflammation and reactions in the skin are evident in both rat and dog. The mechanism underlying these effects is unknown. A comparison with other similar substances indicates that other kinases related to the MAPK pathway and angiogenesis may be involved. Furthermore, skin findings in patients treated with ripretinib are common. The mechanism remains unclear but is not at this point further pursued.

The applicant has defined the toxicological profile of ripretinib in the repeat dose toxicity studies, which in the case of rat species, skin, hair or teeth were identified as target organs. Also, an increase in lung weight, especially in females was reported. According to the applicant this is likely an effect of ripretinib on PDGFR. PDGFR inhibition has been described to affect fluid retention and patients receiving PDGFR inhibitors can develop oedema. The differences observed between male and female animals may be due to different levels of metabolizing enzymes resulting in higher plasma exposures in females.

The microscopic evaluation of the rodent teeth showed minimal to marked degeneration of incisor teeth and loss and/or disorganization of odontogenic cells, changes in dentin. Rodent incisors continue

to grow and differentiate throughout life and is renewed every 40-50 days. Rodent molars grow only little. Thus, the effect on non-growing teeth as in adult patients is most probably limited. The ripretinib-related increased osteoblastic surface and/or decreased trabeculae of the femur observed in rat is also of limited relevance for adult patients since the rodent bone continues to grow into adulthood. However, if treatment is considered for younger patients, the possible effect on teeth and growing bone needs to be taken into consideration.

Values for systemic exposure in patients at the recommended dose of 150 mg ripretinib was initially presented as AUC0-12 h 5678 ng*h/mL for ripretinib and 7138 ng*h/mL for the metabolite DP-5439. The provided calculations were not agreed upon. It should be noted that the exposure margins should be calculated based on the total daily exposure, not on AUC0-12 h as has been done. In the non-clinical assessment the AUC inf values from the single dose study (DCC-2618-01-002) are used (by the CHMP) for the calculations of exposure margins. During the first round of the procedure the applicant updated the values used for exposure margin calculations as well as the exposure margins. The updated values were based on AUC0-inf and resulted in 9856 and 8146 ng•h/mL for ripretinib and DP-5439, respectively. The revised margins did not change the conclusion that exposure margins between NOAEL and patient exposures were below 1.

It is noted that ripretinib displays a more limited nonclinical safety profile in comparison to other TKIs approved for GIST for which e.g. kidney, gastrointestinal and bone marrow effects are commonly seen. Upon request the applicant discussed this further and presented a summary of non-clinical safety findings for the previously approved TKIs for GIST; avapritinib, imatinib, sunitinib, and regorafenib. It is agreed that the skin reactions in dogs treated with ripretinib might be the reason for the more limited nonclinical safety profile of ripretinib in dogs than with other approved TKIs. A better comparison between the different TKIs would demand exposure data, which is not publicly available for all the TKIs. Thus, it is possible that the severe dose limiting dermal effects hampers the identification of toxicity that could have occurred at higher doses. Carcinogenicity studies have not been conducted with ripretinib. New primary malignancies; cutaneous squamous cell carcinomas (CuSCC), was reported in patients treated with ripretinib. Squamous cell carcinoma of skin is classified as an important identified risk in the RMP. CuSCC is also included in the proposed SmPC section 4.4 and 4.8. The lack of carcinogenicity studies is acceptable and according to the ICH S9 guideline. It is stated in the SmPC section 5.3 that no carcinogenicity studies have been conducted.

No fertility and early embryonic development studies were conducted with ripretinib. The lack of dedicated studies on fertility and early embryonic development is acceptable. However, in the 13 weeks repeat-dose toxicity study in rats, minimal to marked bilateral degeneration/atrophy of the testis and increased cellular debris of the epididymis was observed in male rats administered ripretinib 30 and 300 mg/kg/day with no apparent reversibility. Since the recovery period was 28 days and the spermatogenic cycle in rats is approximately 52 days, reversibility might not be expected. In response to a question in the first round of the procedure, the applicant further discussed the findings in male reproductive tissues in rats treated with ripretinib. In studies with other tyrosine kinase inhibitors similar findings have been observed. The specific mechanism of action has however not been investigated. A plausible explanation however is an on-target effect associated with inhibition of the tyrosine receptor kinase KIT. KIT signalling plays an important role in controlling cell proliferation, differentiation, survival, and apoptosis. Attenuation of its signalling strength has been linked to human male infertility (Sandlow et al. 1996), which is not unexpected since cell survival and proliferation are essential for the production of male germ cells (Cardoso et al. 2014). c-KIT is expressed in male germ cells during all stages of spermatogenesis, including post-testicular events related to sperm maturation. No treatment-related effects of ripretinib was seen on the female reproductive tissues. In the other approved TKIs such effects have been observed. The applicant's conclusion; that the risks to female fertility resulting from treatment with ripretinib cannot be completely ruled out, is agreed.

Taken together, the data suggests a potential adverse effect on fertility in patients. This is included in the SmPC section 4.6.

Regarding the product information on pregnancy and lactation (section 4.6). The applicant has provided a justification regarding the duration of which effective contraception should be used after the final dose of ripretinib. The proposed duration is one week, and it is based on the t1/2 of ripretinib (15 h) and DP-5439 (18 h). Thus, the one week is deemed as a sufficient duration.

The applicant had also proposed a recommendation given to treated men with partners of reproductive potential, to use effective contraception. The applicant has provided no data or discussion if this recommendation is based on possible effects on the sperm quality or if it is based on possible transfer of ripretinib to the female partner via semen. However, based on the proposed duration of contraception after the last dose (1 w) which covers 5 half-lives of ripretinib the CHMP's interpretation is that the purpose of recommendation is a precautionary measure to minimize risk for exposure to a female partner and importantly a potential embryo/fetus via semen. Given the teratogenic and embryotoxic potential of ripretinib this could be acceptable. Yet, in many cases the risk for significant exposure via semen is low and the applicant was again asked to justify this recommendation and since no data is available, to base the recommendation on the current scientific knowledge. The applicant did not provide any further scientific rationale behind the recommendation and the recommendation is based on precautionary measures only. This could however be considered acceptable due to the potent developmental toxicity effect of ripretinib. The exposure margin based on AUC at NOAEL in the pivotal embryo-foetal development study in rat vs clinical exposure in humans was 0.02.

Regarding impurities, rat and dog toxicity studies were used to calculate exposure margins. According to the analytical certificates for the 4 weeks studies in rat and dog the batch of the test item was BREC-0809-082 not BREC-0809-092 as stated in Module 3.2.S.3.2 and 3.2.P.5.5. Furthermore, the retention times and area % are slightly different. The different impurities are not identified. In the 13-weeks studies in rat and dog, the presented data in the study reports corresponds to the data presented in Quality Modules. During the first round of the procedure, the applicant has clarified the confusion regarding the information of the batches of the used test items. The specified drug substance impurities can be considered adequately qualified at the proposed specification limits.

The applicant refers to an in silico assessment of the genotoxic potential of four impurities. No mutagenic risks were observed. The reports from this analysis could not be found in the dossier. The applicant claims that the reports have been submitted but the reports could not be located. The study report has been submitted upon request.

The severe dermal effects observed in animals needs also to be taken into consideration in the assessment of the phototoxic potential. It could be questioned if an in vivo study could significantly add to the safety evaluation of ripretinib. Nevertheless, the applicant was in the first round of the procedure requested to justify the absence of a follow-up assessment regarding phototoxicity according to the ICH S10 and the CHMP SA provided in the issue. Any data indicative of phototoxicity from the clinical studies should also be presented. The applicant has tried to justify the absence of a follow up on the positive result in the 3T3 NRU assay. The justification is basically that there is no need for a follow up. This statement is in contrast to the ICH S10 Guidance on photosafety evaluation of pharmaceuticals as well as the advice given by CHMP. The applicant concludes that the evidence and clinical experience are inconclusive and that it seems difficult to speculate to any phototoxicity risk in patients treated with ripretinib. However, it is considered unlikely that the currently proposed precautionary measures would be removed as a consequence of a negative in vivo phototoxicity study since photosensitivity reactions have been observed in 2 patients. Furthermore, similar restrictions are included for substances in the same class.

The proposed text in the SmPC section 4.4 and the inclusion of phototoxicity as an important potential risk in the RMP is thus acceptable and no in vivo phototoxicity study is requested.

2.3.6. Conclusion on the non-clinical aspects

The review of non-clinical data available for ripretinib indicates no major issues for concern. The CHMP considers the following measures necessary to address the non clinical issues: A request to submit an experimentally determined LogKow which the applicant has stated to be submitted post approval in March 2022.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

- Tabular overview of clinical studies

Report Number (Status)	**Study Design**	**Population; N (M/F), Mean (SD) Age**	**Dosing Regimen**	**Study Start/Status**	**Included in MAA and Data Cutoff Date**
DCC-2618-01-001 (ongoing)	Phase1, multi-center, open-label, consisted of a dose Escalation Phase and an Expansion Phase	Patients with advanced malignancies; Age: ≥ 18 years N = 237 (147M/90F), 59.9 (12.36) years. First patient in: 12 Nov 2015. Last patient out (estimated date): 30 Mar 2022	Escalation Phase (28-day cycles): 20, 30, 50, 100, 150, 200 mg BID or 100, 150, 250 mg oral, QD Expansion Phase (28-day cycles): 150 mg, oral, QD; dose could be escalated to 150 mg oral, BID	November 2015 Escalation: Enrolment completed Expansion: Enroling; study ongoing[a].	Yes (as an interim CSR) 01 Mar 2019 for clinical pharmacology data
DCC-2618-01-002 (completed)	Phase 1, randomized, open-label, single-dose, partial	Healthy subjects; 50 mg: N = 40 (21M/19F),	Single dose of 50 or 150 mg (originally designed but not analyzed	February 2019 Enrolment completed;	Yes (as a Full CSR)

Report Number (Status)	Study Design	Population; N (M/F), Mean (SD) Age	Dosing Regimen	Study Start/Status	Included in MAA and Data Cutoff Date
	replicate, 3-period, crossover	35.2 (10.24) years; 150 mg: N = 10 (6M/4F), 39.4 (11.94) years First subject in: 15 Feb 2019 Last subject out: 25 Jun 2019	for bioequivalence) in 3 sequences (1:1:1) with 2 reference formulation periods and 1 test formulation period for each sequence	study completed.	
DCC-2618-01-003 (completed; Module 5.3.3.4)	Phase 1, 2-part, fixed-sequence, open-label, single-dose	Healthy subjects; Age: 18-55 years Cohort 1 (ripretinib + itraconazole): N = 20 (11M/9F), 32.6 (10.28) years; Cohort 2 (ripretinib + pantoprazole): N = 25 (12M/13F), 33.6 (13.57) years. First subject in: 21 May 2019 Last subject out: 08 Aug 2019	Cohort 1: Single dose 50 mg oral in the absence and then presence of 200 mg oral QD itraconazole Cohort 2: Single dose 50 mg oral in the absence and then presence of 40 mg oral QD pantoprazole	May 2019 Enrolment completed; study completed	Yes (as a Full CSR)
DCC-2618-03-001 (INVICTUS) (ongoing; Module 5.3.5.1)	Phase 3, 2-arm, randomized, placebo-controlled, double-blind, international, and multi-center	Patients with advanced GIST who have received treatment with prior anticancer therapies; Age: ≥ 18 years N = 129 (85 in ripretinib group and 44 in placebo group, 73M/56F), 60.1 (11.84) years.	150 mg QD or matching placebo (2:1; 28-day cycles); dose could be kept at/crossed over to 150 mg QD, escalated to 150 mg BID, or discontinued, upon disease progression	February 2018 Enrolment completed; Study ongoing	Yes (as a Full CSR) 31 May 2019 for clinical pharmacology data

Report Number (Status)	Study Design	Population; N (M/F), Mean (SD) Age	Dosing Regimen	Study Start/Status	Included in MAA and Data Cutoff Date
		First patient in: 27 Feb 2018. Last patient out (estimated date): Not applicable because OS is an endpoint.			
DCC-2618-01-006	Phase 1, single-sequence, open-label	healthy adult subjects	Ripretinib 100 mg single dose Rifampicin 600 mg QD	Completed	Yes, at D150

There are 3 additional studies of ripretinib currently ongoing:

- DCC-2618-03-002 (INTRIGUE), a Phase 3 open-label randomised, multi-centre study of ripretinib (150 mg QD) versus sunitinib in patients with advanced GIST after treatment with imatinib (2nd line GIST). This study is ongoing (n=453).

- DCC-2618-01-004, a Phase 1 study of the PK, safety, and tolerability of ripretinib (50 mg) in subjects with hepatic impairment compared to healthy controls. This study is ongoing.

- DCC-2618-01-007, a Phase 1, open-label study to evaluate the effects of ripretinib (150 mg QD) on the PK of repaglinide (0.5mg, a CYP2C8 probe substrate) in patients with advanced GIST. This study is ongoing.

2.4.2. Pharmacokinetics

Ripretinib (also known as DCC-2618) is a new chemical entity and the pharmacokinetic studies should thus aim at describing the disposition and also to identify subgroups where an increased or decreased exposure can be expected based on the pharmacokinetic properties. Potential interactions based on the pharmacokinetic properties should also be evaluated.

Ripretinib is a lipophilic, weak base compound, in a highly crystalline form that is practically insoluble in aqueous media. Ripretinib is an inhibitor of tyrosine-protein kinase (KIT) and of platelet-derived growth factor alpha (PDGFRA) kinase. The sought indication is for the treatment of adult patients with advanced gastrointestinal stromal tumour (GIST) who have received prior treatment with kinase inhibitor therapies. The recommended dosage of ripretinib is 150 mg (three 50 mg tablets) taken orally once daily at the same time each day with or without food. The recommended dose reduction for adverse reactions is 100 mg orally, once daily.

PK data for ripretinib and DP-5439 is currently available from 4 clinical studies and numerous in vitro studies. All PK studies were conducted according to GCP.

The major metabolic pathway of ripretinib is N-demethylation to form an active metabolite known as DP-5439. DP-5439 has a similar pharmacologic activity to ripretinib on both KIT and PDGFRA.

The active moiety (based on ripretinib and DP-5439) is used for correlations to efficacy, while for safety both ripretinib and DP-5439 each and combined as the active moiety are considered. The therapeutic window is currently not clearly defined, but dose adjustments are foreseen in case of adverse events.

Methods

Bioanalysis

Ripretinib and its active metabolite DP-5439 were quantified by LC-MS using validated methods in human K_2EDTA plasma, urine and faeces.

Pharmacokinetic data analysis

A non-compartmental analysis and a population PK analysis were used.

The population PK analysis and PK/PD modelling was conducted via nonlinear mixed-effects modelling with the NONMEM software. The first-order conditional estimation method of NONMEM with interaction (FOCE INTER) method was used for model development. R version 3.4.4 was used for simulations.

The population PK model was developed PK from 350 patients pooled from Studies DCC-2618-01-001 and DCC 2618-03-001 (Invictus)with a total of 5587 PK observations of each ripretinib and DP-5439. There were 303 (5.4%) BLQ ripretinib concentrations, 423 (7.6%) BLQ DP-5349 observations, and 4 (0.1%) DP-5439 concentrations above the assay limit of quantification (ALQ). The BLQ and ALQ concentrations were treated as missing.

A covariate analysis was conducted to assess the sources of variability in ripretinib PK using a full model approach with backward elimination. Candidate covariate-parameter selections were chosen based on evaluation of random effect vs. covariate plots and on clinical relevance. The candidate covariate-parameter relationships were added simultaneously to the base model, resulting in the full model. Model covariate relationships dropped from the full model using a backward elimination method based on a statistical significance level of $p < 0.005$. Highly correlated covariates (e.g., absolute value of correlation coefficient > 0.3) were not be included together on the same parameter.

Ripretinib final model

Ripretinib oral PK was described by a 2-compartment model with linear elimination (Population Pharmacokinetic Modeling Report). The absorption phase was described as zero-order drug release followed by first-order absorption with a modest, linear dose-dependent decrease in relative bioavailability (Frel). Food delayed absorption without affecting rate of absorption and increased Frel by increasing dose levels. A high-fat meal also increased Frel, with greater effects on Frel at higher doses and a 36% increase in Frel at 150 mg.

The only covariate effects retained were 29% lower CL/F in females compared to males and 23% higher Ka in patients with prior gastrectomy. However, both were not deemed to be clinically meaningful based on the safety and efficacy E-R analyses.

Table 2: Ripretinib Final Population Pharmacokinetic Model Estimates

Parameter	**Fixed Effects**		**BSV CV%**	
	Estimate	**RSE%**	**Estimate**	**RSE%**
Apparent systemic clearance; CL/F (L/h)	12.7	4.0%	53.6%	3.9%
Apparent central volume of distribution; Vc/F (L)	20.4	8.7%	58.2%	17.5%

Parameter	Fixed Effects		BSV CV%	
	Estimate	RSE%	Estimate	RSE%
Apparent inter-compartmental Clearance; Q/F (L/h)	7.30	3.0%	0 FIXED	NA
Apparent peripheral volume of distribution; Vp/F (L)	675	7.2%	1464.7%	7.3%
First-order absorption rate constant; Ka (1/h)	0.0832	2.7%	43.3%	5.9%
Duration of zero-order release; D1 (h)	1.46	6.6%	71.4%	6.6%
Relative bioavailabilty (Frel) vs. dose slope (1/mg)	-0.00294	8.8%	NA	NA
D1 ~ high-fat meal fold-change	3.47	NA	NA	NA
Frel ~ high-fat meal fold-change, < 100 mg	1.131 FIXED	NA	NA	NA
Frel ~ high-fat meal fold-change, 100 or 150 mg	1.356 FIXED	NA	NA	NA
Frel ~ high-fat meal fold-change, > 150 mg	1.683 FIXED	NA	NA	NA
CL/F ~ female fractional change	-0.287	14.4%	NA	NA
Ka ~ prior gastrectomy fractional change	0.230	40.3%	NA	NA
Proportional residual error (CV%)	41.0%	0.85%	NA	NA
Additive residual error standard deviation (ng/mL)	29.6	1.9%	NA	NA

Abbreviations: BSV = between subject variability; CL/F = apparent systemic clearance; CV% = percent coefficient of variation; D1 = duration of zero-order release; Frel = relative bioavailability; Ka = first-order absorption rate constant; NA = not applicable; Q/F = apparent inter-compartmental clearance; RSE = relative standard error; V_c/F = apparent central volume of distribution; Vp/F = apparent peripheral volume of distribution. Source: Population Pharmacokinetic Modeling Report, Table 11.

DP-5439 final model

Ripretinib concentrations derived from the post hoc (i.e., model-predicted patient-level) 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 the active metabolite of ripretinib, DP-5439, was described as a 1-compartment model with linear elimination, with its formation generated from the central compartment of ripretinib (Table 10). No covariate analysis was performed for DP-5439.

Table 3: DP-5439 Final Population Pharmacokinetic Model Estimates

Parameter	Fixed Effects		BSV CV%	
	Estimate	RSE%	Estimate	RSE%
Metabolite apparent clearance; CLm/F (L/h)	7.29	5.0%	84.8%	4.3%

Parameter	Fixed Effects		BSV CV%	
	Estimate	RSE%	Estimate	RSE%
Metabolite apparent volume of distribution; Vm/F (L)	64.0	5.0%	72.9%	3.8%
Proportional residual error (CV%)	0.4064	0.6%	NA	NA
Additive residual error standard deviation (ng/mL)	26.5	2.7%	NA	NA

Abbreviations: BSV = between subject variability; CLm/F = metabolite apparent clearance; CV% = percent coefficient of variation; NA = not applicable; RSE = relative standard error; Vm/F =metabolite apparent volume of distribution. Source: Population Pharmacokinetic Modeling Report, Table 12.

Simulations

The reference patient was defined as a male patient without prior gastrectomy taking the clinical dose of 150 mg QD ripretinib in the fast ed state. AUC values for the different scenarios displayed were derived from 1500 simulated replicates that incorporated BSV. The median simulated ripretinib AUC,ss for the reference patient was 11.6 µg*h/mL and 19.9 µg*h/mL for DP-5439.

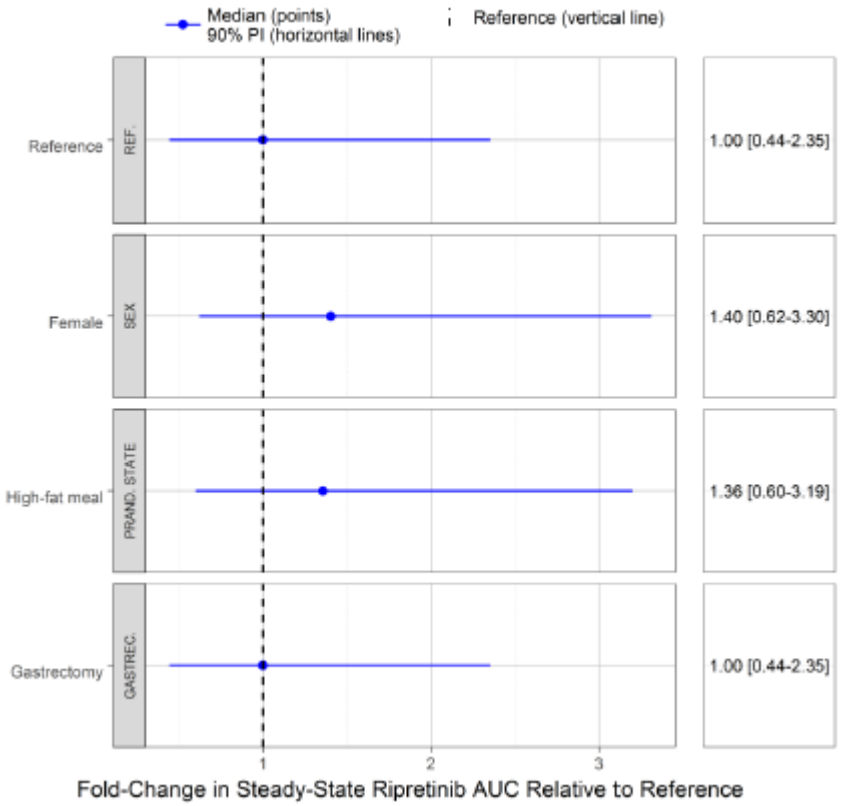


Figure 2: Forest Plot of Covariate Effects on Ripretinib Steady-State AUC for the reference patient given 150 mg ripretinib QD. Numbers in the right-hand panel represent median [90% PI].

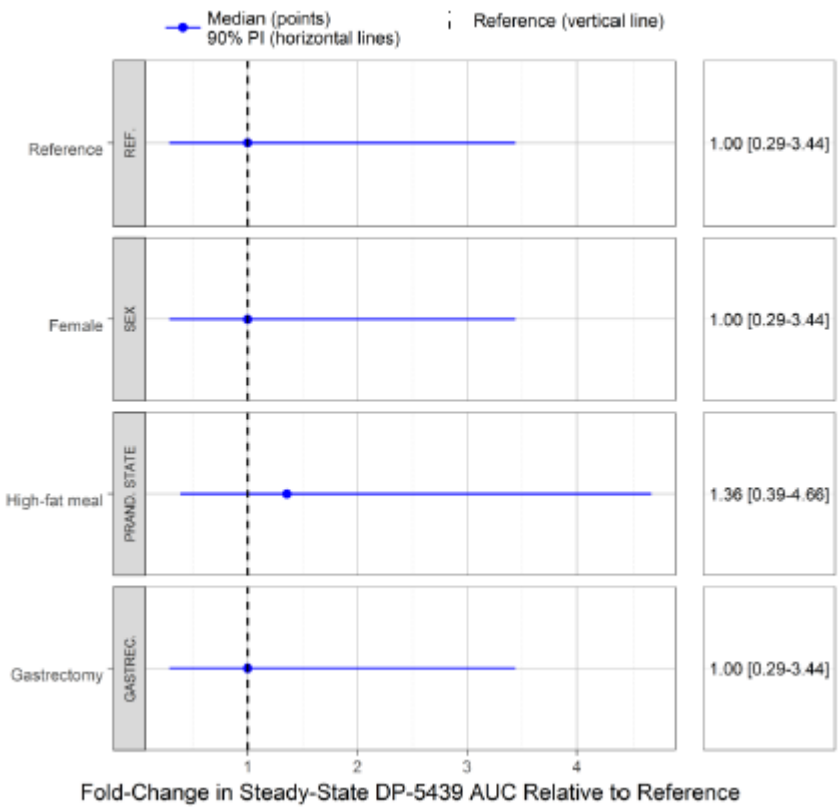


Figure 3: Forest Plot of Covariate Effects on DP-5439 Steady-State AUC for the reference patient given 150 mg ripretinib QD. Numbers in the right-hand panel represent median [90% PI].

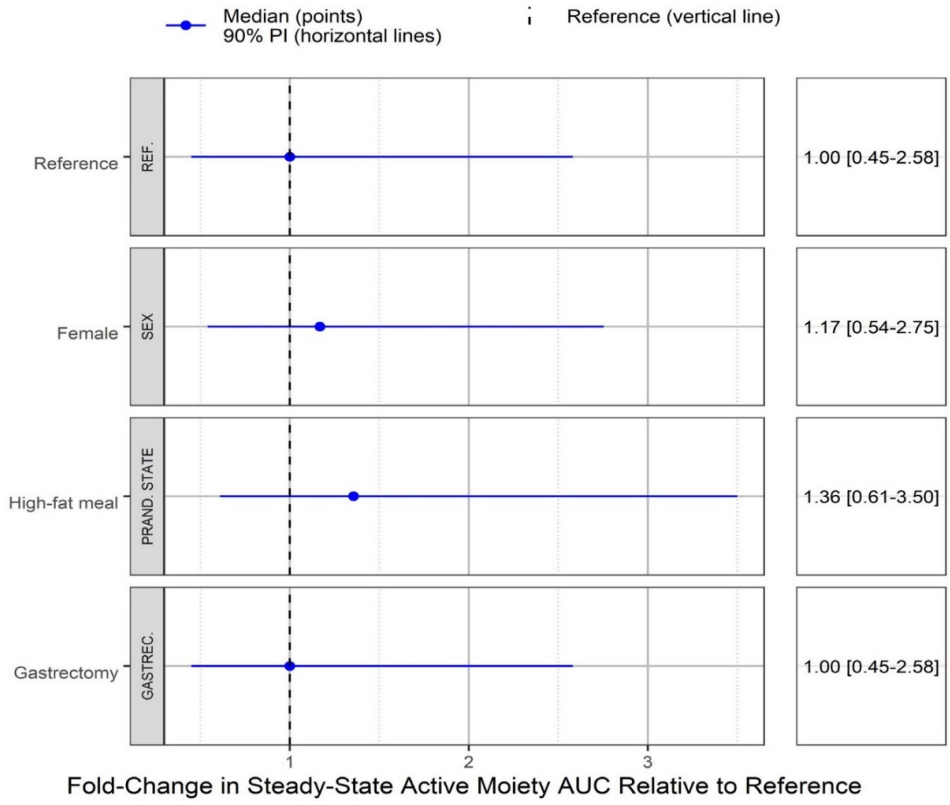


Figure 4: Forest Plot of Covariate Effects on the Active Moiety Steady-State AUC for the reference patient given 150 mg ripretinib QD. Numbers in the right-hand panel represent median [90% PI].

Ripretinib AUC_{SS} following 150 mg QD was predicted to be 40% higher in females compared to males, but a negligible effect of sex on DP-5439 exposure was predicted. The effect of prior gastrectomy on ripretinib and DP-5439 exposures was predicted to be minor (no effect on AUC and a 9% increase in ripretinib maximum concentration). Relative to 150 mg QD administered in the fasted state, 150 mg QD administered with a high-fat meal was predicted to result in a 36% increase in AUC. Based on the exposure-response analyses, the effects of sex and ripretinib administration with a high-fat meal are not expected to be clinically meaningful.

No clinically meaningful differences in the PK of ripretinib were observed based on age (19 to 87 years), sex, race (White, Black, and Asian), body weight (39 to 138 kg), tumour type (GIST or other solid tumour), prior gastrectomy, mild to moderate renal impairment (CrCL 30 to < 90 mL/min), and mild hepatic impairment (NCI hepatic impairment categories B1 and B2).

There were insufficient data for an assessment of the effect of severe renal impairment and moderate/severe hepatic impairment with only 2 (0.571%) patients with moderate hepatic impairment, no patients with severe hepatic impairment, and only 4 (1.14%) patients with severe renal impairment.

Absorption

Ripretinib is a substrate of PgP, and data are inconclusive for BCRP. DP-5439 is a substrate of both PgP and BCRP.

Ripretinib has low solubility and is thus a BCS class II or IV compound. An absolute bioavailability study has not been performed.

Bioequivalence was demonstrated between the clinical process formulation and the commercial formulation using the 50 mg dose. Ratios (test: reference) of least squares means (LSMs) for AUC0-t, AUC0-∞, and Cmax were 107.20%, 106.71%, and 105.78%, respectively, with each 90% confidence interval (CI) falling within 80% to 125%. Data for 150 mg from study DCC-2618-01-002 is presented in Table 11, as it is included in the SmPC. The dataset is however not powered for conclusions on bioequivalence.

Table 4: Summary of Plasma Pharmacokinetic Parameters of Ripretinib following a Single Oral Administration of 150 mg Ripretinib Test or Reference Formulation in Healthy Subjects

PK Parameters[a]	**150 mg Test (n = 7)**	**150 mg Reference (n = 14)**	**150 mg Test (n = 7)**	**150 mg Reference (n = 14)**
Analyte	**Ripretinib**		**DP-5439**	
AUC_{0-t} (ng×h/mL)	9753.0 (43.5)[b]	9662.4 (44.9)[c]	7959.3 (55.2)	8432.9 (63.4)
$AUC_{0-\infty}$ (ng×h/mL)	9855.8 (38.9)	9818.0 (45.2)[c]	8146.2 (55.8)	8361.7 (62.7)
C_{max} (ng/mL)	592.3 (31.3)	677.6 (36.5)	246.2 (32.8)	280.5 (30.4)
t_{max} (h)[d]	4.00 (3.00, 8.00)	4.00 (2.00, 8.00)	8.00 (4.00, 24.18)	5.00 (3.02, 12.00)
$t_{½}$ (h)	12.636 (16.7)	14.751 (30.3)[c]	15.629 (23)	17.755 (23.3)
CL/F (L/h)	15.22 (38.9)	15.28 (45.2)[c]	17.91 (55.8)	17.45 (62.7)

PK Parameters[a]	150 mg Test (n = 7)	150 mg Reference (n = 14)	150 mg Test (n = 7)	150 mg Reference (n = 14)
Analyte	**Ripretinib**		**DP-5439**	
V_z/F (L)	277.46 (41.4)	325.13 (51.5)[c]	403.78 (49.1)	446.87 (74)
V_{ss}/F (L)	302.17 (34.9)	307.29 (38.6)[c]	490.79 (38.1)	507.12 (50.5)

[a]Geometric mean (GeoCV%). [b] n = 6. [C] n = 13. [d] Median (min, max). Source: Study DCC-2618-01-002 CSR, Table 12.

Phase 1 study DCC-2618-01-001 data is included in the pop PK analysis, therefore only selected PK parameters are detailed here, as relevant in the applicants claims, ie 100 mg for dose reductions, 150 mg QD as standard dose and 150 mg BID as used in case of disease progression in the Invictus study.

The key PK findings of the escalation phase are summarised here, in Table 12 and Table 13 for the 100 and 150 mg doses. Following single doses under fasted conditions on Cycle 1 Day 1, ripretinib PK parameters were highly variable between patients, with CV% for Cmax and AUC0-24 ranging from approximately 46% to 60% and 62% to 93% for the corresponding parameters for DP-5439 at ripretinib doses with PK data for at least 10 patients. The median tmax of ripretinib ranged from approximately 2 to 10 hours and 6-24h for DP-5439. After single dose of ripretinib, DP-5439 to ripretinib (metabolite to parent) ratios ranged from approximately 22%-to 92% based on AUC0-t across the studied dose range, with a M:P ratio for AUC0-t at the 150 mg dose of ripretinib of 66%.

Table 5: Summary of Plasma PK Parameters of Ripretinib and DP-5439 Following a Single Oral Administration of Ripretinib in Patients with Advanced Malignancies – Cycle 1 Day 1

Parameter[a]	100 mg (N = 17)[b]	150 mg (N = 23)[b,c]	100 mg (N = 15)	150 mg (N = 21)
Analyte	**Ripretinib**		**DP-5439**	
$AUC_{0\text{-}12\ (}$ng×h/mL)	3677 (48.9)	3769 (59.8)	1943 (80.4)	1696 (65.3)
$AUC_{0\text{-}24}$ (ng×h/mL)	7518 (50)	6678 (61.2)	5229 (88.7)	4086 (62.0)
$AUC_{0\text{-}t}$ (ng×h/mL)	7518 (50)	6678 (61.2)	5229 (88.7)	4086 (62.0)
C_{max} (ng/mL)	521 (46.1)	497 (57.9)	339 (92.5)	233 (65.1)
t_{max} (h)[d]	10.03 (2.00, 24.68)	4.03 (1.95, 24.05)	23.63 (3.83, 24.68)	23.08 (4.00, 24.82)
M:P Ratio $AUC_{0\text{-}t}$			0.7090 (58.3)	0.6566 (54.4)
M:P Ratio C_{max}			0.6641 (52.5)	0.4962 (59.4)

[a]Geometric mean (GeoCV%).[b] Patients from the QD cohort and patients from the BID cohort received only a single dose at C1D1. [c] Escalation and Expansion Phases combined. [d] Median (Min, Max). Sources: Study DCC-2618-01-001

Table 6: Summary of Plasma PK Parameters of Ripretinib and DP-5439 Following Multiple Oral Administrations of Ripretinib in Patients with Advanced Malignancies– Cycle 1 Day 15

Parameter[a]	**100 mg QD (N = 5)**	**150 mg QD (N = 10)**[b]	**150 mg BID (N = 6)**	**100 mg QD (N = 5)**	**150 mg QD (N = 11)**[b]	**150 mg BID (N = 6)**
Analyte	**Ripretinib**			**DP-5439**		
AUC_{0-t} (ng×h/mL)	3212 (80.2)	5892 (31.1)	8614 (88.4)	3545 (187.9)	7329 (45.9)[i]	15221 (94.8)
AUC_{0-12} (ng×h/mL)	3077 (95.7)[c]	5892 (31.1)	7929 (97.7)[d]	3346 (251.6)[f]	7138 (44.4)[i]	15646 (110.3)[d]
C_{max} (ng/mL)	505 (71.8)	775 (33)	1290 (79.1)	471 (218.9)	826 (47.1)[i]	1800 (85.9)
t_{max} (h)[j]	2.00 (0.90, 2.00)	2.07 (1.02, 8.13)	2.01 (0.55, 6.00)	4.00 (0.90, 5.83)	5.01 (1.02, 8.13)[i]	4.01 (2.03, 8.17)
C_{trough} (ng/mL)	173 (184.7)	292 (65.2)[e]	968 (113.8)	291 (358.4)	555 (82.8)	1590 (93.8)
C_{avg} (ng/mL)	256 (95.7)[c]	491 (31.1)	661 (97.7)[d]	279 (251.6)[f]	611 (45.9)[i]	1300 (110.3)[d]
CL_{ss}/F (L/h)	NA	NA	17.4 (109.3)[d]	NA	NA	8.84 (141.8)[d]
RA (AUC_{0-12})	0.997 (48.4)[c]	1.75 (55.2)	2.41 (24.7)[d]	1.60 (152.9)[g]	5.76 (43.1)[h]	7.18 (40.5)[d]
RA (C_{max})	1.12 (38.5)	1.69 (52.6)	2.84 (17.9)	1.84 (116.3)[f]	4.80 (33)[h]	7.36 (44.6)
M:P Ratio AUC_{0-t}				1.14 (80.6)	1.28 (50.6)[i]	1.817 (106.3)
M:P Ratio C_{max}				0.960 (90.4)	1.10 (50.7)[i]	1.442 (105.6)

[a] Geometric mean (GeoCV%). [b] Escalation and Expansion Phases combined. [c] n = 4. [d] n = 5. [e] n = 11. [f] n = 4. [g] n= 3. [h] n = 8. [i] n = 10. [j] Median (Min, Max). Source: Study DCC-2618-01-001

The administration of the intended dose of 150 mg ripretinib with a high-fat meal increased the exposures (AUC_{0-24}) to ripretinib and the metabolite DP-5439 by approximately 30% and 47%, respectively, compared to the fasted condition in study DCC-2618-01-001. Following this, ripretinib was administered regardless of meals in the rest of study DCC-2618-01-001 and in the phase 3 study INVICTUS.

Ratios of ripretinib AUC_{0-24} fed vs fasted were 82%, 81%, 69%, 95% and 154% for 20mg, 30 mg, 50 mg, 100 mg and 200mg respectively, for 3-4 subjects per dose group, with the exception of the 100 mg group with n=14. At 100 mg ripretinib, the ratio of Cmax fed/fasted was 103%.

Distribution

Protein binding of ripretinib was 99.93% in pooled human plasma. Ripretinib was bound to 99.8% to HSA (at both 1 and 10 µM) and to 99.4% and 98.6% for α1-AGP solutions, respectively. For DP-5439, protein binding was 99.7% and 99.6% in HSA and >99.8% and 98.7% in α1-AGP solutions, respectively for 1 and 10 µM. Both parent and metabolite extensively bound to the human plasma proteins, with no concentration dependency in binding to HAS. However, there was a modest concentration dependency in binding to α1-AGP.

Ripretinib primarily partitions to plasma. with mean blood-to-plasma concentration ratios (Cb/Cp) ranging from 0.843 to 0.879 (human 1), 0.736 to 0.867 (human 2), and 0.748 to 0.813 (human 3).

In study DCC-2618-01-002 in healthy subjects, 150 mg ripretinib given as the commercial formulation had a mean (CV%) apparent volume of distribution (Vss/F) of 302 (35%) L for ripretinib and 491 (38%) L for DP-5439. The apparent volume of distribution associated with the terminal phase (Vz/F) was 278 (41%) L for ripretinib and 404 (49%) L for DP-5439 in healthy subjects receiving a single 150 mg dose of ripretinib.

Elimination

In study DCC-2618-01-002 in healthy subjects, 150 mg ripretinib given as the commercial formulation had a mean (CV%) apparent clearance of 15.2 (39%) L/h and 17.9 (56%) L/h for ripretinib and DP-5439, respectively. Mean (CV%) half-life (t½) were 12.6 (17%) and 15.6 (23%) hours for ripretinib and DP-5439, respectively.

Excretion

A mass balance study was not performed as no suitable formulation was deemed suitable. The formulation challenges are 1) the poor solubility of the crystalline form of ^{14}C-labeled ripretinib free base and 2) the infeasibility of spray-drying the radiolabelled crystalline material into amorphous form on hydroxypropyl methylcellulose acetate succinate (HPMCAS) due to its radioactivity. These formulations are not clinically viable due to the decreased exposure observed with both the crystalline free-base form of ripretinib and non-spray-dried dispersion on HPMCAS formulations. In addition, in preclinical species, administration of ^{14}C-labeled ripretinib free base in Labrasol resulted in poor tolerability in rat single dose PK and mass balance studies.

In study DCC-2618-01-003 cohort 2, a single oral dose of 50 mg unlabelled ripretinib was given to healthy subjects under fasting conditions. Human plasma, urine and faecal samples were collected from 10 healthy subjects through 1 week (168 hours). Cumulative recovery of ripretinib and its active metabolite DP-5439 in both urine and faeces appeared to plateau during the 1-week collection period. Excretion of metabolites other than DP-5439 in faeces were not evaluated. Through 1 week (168 hours) after a single oral administration of 50 mg ripretinib (given alone), 0.0216% of the ripretinib dose was excreted unchanged in urine and 34.21% of the ripretinib dose was excreted unchanged in faeces, while 0.1044% of the ripretinib dose was excreted as metabolite DP 5439 in urine and 5.910% in faeces. For combined ripretinib and DP-5439, 0.126% of the ripretinib dose was excreted in urine and 40.12% in faeces.

The mean apparent renal clearance (CLr/F) for ripretinib (3.06 mL/h) was lower compared to the mean plasma clearance (13.55 L/h). The mean CLr/F for DP-5439 (18.0 mL/h) was also lower compared to the mean apparent systemic clearance (CL/F, 18.54 L/h). This suggested that the systemic elimination of ripretinib and DP-5439 was not primarily attributed to the kidney.

The clinical results are consistent with pre-clinical absorption, distribution, metabolism, and excretion (ADME) studies with [^{14}C]-ripretinib where > 88% of the radiolabelled oral dose to rats and

intravenous (IV) dose in dogs were recovered in the faeces, while less than 1% of the administered IV dose to dogs was recovered in the urine (Studies DCC-2618-03-0037 and DCC-2618-03-0038).

Metabolism

The metabolism of ripretinib was investigated in several in vitro studies and an in vivo study with unlabelled ripretinib. The main elimination pathway for ripretinib is via N-demethylation to DP-5439, which possesses similar pharmacological activity. In vitro metabolic identification suggested that ripretinib was mainly metabolized by CYP3A4 but also to a minor extent by CYP2C8 and CYP2D6. CYP3A4 was the major pathway in the metabolism of DP-5439. In addition, CYP1A2, CYP2E1, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 each may also play a role in the metabolism of DP-5439.

Genotyping for CYP2D6 in a subset (n=46) of patients in the PK population of study DCC-2618-01-001 did not reveal any trend in AUC0-24 or Cmax of ripretinib and DP-5439.

Aside DP-5439, five further metabolites were observed in vitro. DP-5439 and six further metabolites were observed in plasma and urine and each of the six remaining metabolites was excreted as <1% of the (unlabelled) dose. Apart from DP-5439, only M1 and M3 were detected both in vitro and in vivo, and only M1 and DP-5439 were found both in plasma and urine.

The systemic exposure of the main plasma metabolite DP-5439 was in the same range as ripretinib and was studied in all clinical studies.

Dose proportionality

Dose proportionality was assessed with data from study DCC-2618-01-001, with ripretinib doses of 20 mg BID to 200 mg BID, and 100 mg to 250 mg QD at C1D1 and C1D15. Data included in the analysis was in fasted state. Across the dose range of 20-250 mg, ripretinib and DP-5439 PK appeared to be less than dose proportional, especially at ripretinib doses higher than 150 mg.

Time dependency

Time dependency was evaluated at C1D15 using Cmax and AUC0-12 in study DCC-2618-01-001. At Cycle 1 Day 15, for ripretinib, the accumulation ratios for AUC0-12 and Cmax were 1.66 and 1.61, respectively, when compared to the Cycle 1 Day 1 for ripretinib 150 mg QD. For DP-5439, a 5.29-fold accumulation for AUC0-12 and a 4.57-fold accumulation for Cmax were observed when compared to the Cycle 1 Day 1 for ripretinib 150 mg QD, with a geometric mean M:P ratio of 1.29 based on AUC0-t.

For the 150 mg QD regimen in the Expansion Cohort (n=130) in study DCC-2618-01-001, accumulation estimates ranged from approximately 1.4 to 1.9 calculated with AUC0-6. There was no evidence of time dependency in trough concentrations. Steady-state conditions appears to be achieved within 14 days.

Intra- and inter-individual variability

In the pop PK analysis, interindividual variability was 54% on CL/F, 58% on Vc/F, 1465% on Vp/F, 43% on Ka and 71% on the duration of the zero order release for ripretinib. Intra individual variability for ripretinib was 41%. Similarly high variability was observed in NCA data from study DCC-2618-01-001.

For DP-5439, interindividual variability was 85% on CL_M/F and 73%% on Vc_M/F. Intra individual variability for DP-5439 was 41%.

Pharmacokinetics in target population

All studies were performed in patients, except for study DCC 2618 01-002 (bioequivalence) and study DCC 2618 01-003 (DDI) in healthy subjects. An informal cross-study comparison indicates that

ripretinib and DP-5439 Cmax and AUC following single doses of ripretinib are generally similar between GIST patients in Study DCC 2618-01-001 compared to the healthy subjects in Study DCC 2618 01-002.

Data from the phase 3 study DCC-2618-03-001 (INVICTUS) is included in the pop PK analysis and consists primarily of trough concentrations of ripretinib and DP-5439.

Special populations

Impaired renal function

The renal recovery from Study DCC-2618-01-003 suggested that renal elimination does not play an important role in the excretion of ripretinib. Based on the population PK analysis, ripretinib and DP-5439 PK exposure in patients with mild or moderate renal impairment (baseline creatinine clearance [CrCL] 30 to < 90 mL/min) is similar with that in patients with normal renal function for ripretinib 150 mg QD.

Data in patients with severe renal impairment is scarce, thus a new cohort in patients with CrCL between 20 and 50 mL/min will study exposure levels, tolerability and patient safety in the ongoing study DCC-2618-01-001.

Impaired hepatic function

Ripretinib and DP-5439 are metabolised predominantly by CYP3A4, hence hepatic impairment may impact ripretinib PK. Based on the population PK analysis, ripretinib and DP-5439 PK exposure in patients with mild hepatic impairment (National Cancer Institute [NCI] hepatic impairment category B) is similar with that in patients with normal hepatic function for ripretinib 150 mg QD. The impact of moderate to severe hepatic impairment on the PK of ripretinib is unknown and will be studied in the ongoing dedicated hepatic impairment study DCC-2618-01-004.

Gender & Weight

Ripretinib AUC_{SS} following 150 mg QD was predicted to be 40% higher in females compared to males, but a negligible effect of gender on DP-5439 exposure was predicted. Body weight (39 to 138 kg) was not a significant covariate in the population PK analysis.

Race & Age

Race and age (18 to 87 years) were not significant covariates in the population PK analysis (White, 78%; Black, 7.7%; Asian, 5.7%; American Indian or Alaskan native, 0.86%; other, 4.3%; and missing, 3.4%). Ripretinib is not intended for children and has a PIP waiver for studies in paediatric patients.

Numbers of Patients by Age group Used in Population PK Modelling

Study	**Age <65y n (%)**	**65y ≥ Age ≤74y n (%)**	**75y ≥ Age ≤84y n (%)**	**Age ≥ 85y n (%)**
DCC-2618-01-001 (N=237)	152 (64.1)	55 (23.2)	26 (11.0)	4 (1.7)
DCC-2618-03-001 (N=113)	68 (60.2)	30 (26.5)	15 (13.3)	0

Overall (N=350)	220 (62.9)	85 (24.3)	41 (11.7)	4 (1.1)

Abbreviations: PK=pharmacokinetic; y=years

Interactions

Effect of other medicines on ripretinib

Ripretinib and DP-5439 are substrates of CYP3A4/5. CYP2C8 and CYP2D6 also play a role in the metabolism of ripretinib. In addition, CYP1A2, CYP2E1, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 each may also play a role in the metabolism of DP-5439.

Ripretinib and DP-5439 are substrates of PgP and BCRP. Data for ripretinib and BCRP are currently inconclusive though. Ripretinib and DP-5439 were not substrates of OATP1B1, 1B3, OAT1 (DP-5439), OAT3, OCT1 (ripretinib), OCT2, BSEP (DP-5439), MATE1 or MATE2-K (parentheses indicate that data was available only for one of ripretinib or DP-5439).

The effects of concomitant administration with the PgP and CYP3A4 inhibitor itraconazole were studied in vivo. Ratios of geometric LS means for plasma ripretinib AUC0-t, AUC0–∞, and Cmax were 198.36%, 198.74%, and 135.71%, respectively, for ripretinib with itraconazole relative to ripretinib alone. For DP-5439 AUC0-t, AUC0–∞, and Cmax ratios were 194%, 199%, and 106%, respectively, for ripretinib with itraconazole relative to ripretinib alone. For the active moiety AUC0-t, AUC0–∞, and Cmax ratios were 198.50%, 202%, and 127%, respectively, for ripretinib with itraconazole relative to ripretinib alone.

Concomitant administration of the CYP3A4 inducer rifampicin 600mg QD decreased the mean AUCs of both ripretinib and DP-5439 or the combined ripretinib+DP-5439 by approximately 60%, compared with administration of ripretinib alone. The effects of rifampicin on Cmax were smaller in magnitude and divergent for ripretinib (decreased by 18%) versus DP-5439 (increased by 37%), but the Cmax for ripretinib combined with DP-5439 was similar with and without rifampicin.

The effects of concomitant administration of PPI were studied in vivo with pantoprazole. Ratios of geometric LS means for plasma ripretinib AUC0-t, AUC0-∞, and Cmax were 109.01%, 109.32%, and 103.23%, respectively, for ripretinib with pantoprazole relative to ripretinib alone. For DP-5439 AUC0-t, AUC0-∞, and Cmax, these were 130.96%, 130.13%, and 112.28%, respectively, for ripretinib with pantoprazole relative to ripretinib alone. For combined ripretinib and DP-5439 AUC0-t, AUC0-∞, and Cmax, these were 116.33%, 116.58%, and 103.76%, respectively, for ripretinib with pantoprazole relative to ripretinib alone.

Effect of ripretinib on other medicines

The in vitro inhibition data by ripretinib and DP-5439 is summarised in the table below:

	Ripretinib	**DP-5439**
	Ki (µM)	**Ki (µM)**
Enzymes		
CYP1A2	> 7	> 7
CYP2B6	> 7	> 7
CYP2C8	0,06	0,15

CYP2C9	0,17*	0,7*
CYP2C19	0,33*	0,35*
CYP2D6	0,9	1,0
CYP3A	> 7, TDI: K_I 2.5 µM	> 7
Transporters (demanded)		
P-gp	0,98	> 7
BCRP	0,02	0,63
OATP1B1	> 100	73% inhibition at 7 µM
OATP1B3	40% inhibition at 3 µM, 89% inh at 100 µM	> 7
OAT1	> 10	> 7
OAT3	> 100	> 7
OCT2	> 3	> 7
Transporters (optional)		
OCT1	> 100	na
MATE1	> 3	0,355
MATE2-K	> 3	> 1,5
BSEP	0,82	> 7

Assuming Ki = IC50/2 * lowest of 2 independent experiments

No time-dependant inhibition was observed, except for CYP3A4. K_I of CYP3A4 inhibition by ripretinib (using midazolam as the substrate) was determined as 2.5 ± 0.9 µM, with kinact 0.0034 ± 0.0005 min^{-1} and kinact/K_I 1.4 min^{-1} mM^{-1}.

The mechanistic static model was used to assess the inhibition of CYP2C8, 2C9, 2C19 and 2D6 by ripretinib, using Ki listed in the table above. AUCR were 1.31, 1.08, 1.06 and 1.02, respectively.

An in vivo study with repaglinide, as a sensitive substrate of CYP2C8, is ongoing. No other studies are planned.

CYP3A4 and 2B6 induction by ripretinib and DP-5439were observed. A ripretinib and DP-5439 concentration-dependent decrease of CYP1A2 mRNA was observed.

Exposure relevant for safety evaluation

Ripretinib

The ripretinib Cmax,ss relevant for safety is taken from study DCC-2618-01-001 at C1D15 150 mg ripretinib given under fasting conditions and is 761 ng/mL. Only AUC_{0-12} is reported in that study.

In study DCC-2618-01-002, where a single dose of 150 mg ripretinib as commercial formulation was given in fasted state, AUC_{inf} was 9855.8 ng*h/mL. In the pop PK analysis, the median simulated ripretinib AUC,ss for the reference patient was 11600 ng*h/mL.

DP-5439

The DP-5439 Cmax,ss relevant for safety is taken from study DCC-2618-01-001 at C1D15 150 mg ripretinib given under fasting conditions and is 804 ng/mL. Only AUC_{0-12} is reported in that study.

In study DCC-2618-01-002, where a single dose of 150 mg ripretinib as commercial formulation was given in fasted state, AUC_{inf} was 8146.2 ng*h/mL. In the pop PK analysis, the median simulated DP-5439 AUC,ss for the reference patient was 19900 ng*h/mL.

2.4.3. Pharmacodynamics

Exposure/response

QT

An evaluation of the concentration-QTc relationship for ripretinib was conducted based on time matched ECG-concentration measurements in the escalation cohort of Study DCC 2618 01-001. Ripretinib doses ranged from 20 to 200 mg BID and 100 to 250 mg QD, including clinical dose of 150 mg QD for 18 patients and above-the-daily clinical doses for 23 patients. Both the by-timepoint and the concentration-QTc analysis demonstrated that ripretinib at the studied doses did not cause clinically relevant QT prolongation. The relationship between the ΔQTcF and concentrations of ripretinib were investigated by linear mixed effects modelling.

The estimated population slope of the ripretinib concentration-QTc relationship was shallow and slightly negative. The predicted ΔQTcF at ripretinib Cmax at 150 mg QD is -8.97 ms (90%CI -10.43; -3.41) for a Cmax of 840.8 ng/mL (90% CI 706.04 -1001.35).

The estimated population slope of the DP-5439 concentration-QTc relationship was negative and statistically significant. The predicted ΔQTcF at DP-5439 Cmax when given 150 mg ripretinib QD is -7.28 ms (90%CI -10.37; -4.18) for a Cmax of 717.7 ng/mL (90% CI 538.18 -957.14).

Exposure response modelling

Observed average trough concentrations (Cmin) of ripretinib, DP-5439, and combined ripretinib + DP-5439 up to the time of the adverse event (AE; for safety endpoints) or up to the time of disease progression/death or censoring (for PFS) were calculated using observed trough concentrations. Cmin was used to perform exposure-response analyses for safety for patients in Study DCC-2618-01-001 and the invictus trial and for efficacy (i.e., PFS) for patients in the invictus trial. Combined ripretinib and DP-5439 exposure was the sum of ripretinib and DP-5439 exposure with a molecular weight correction.

Safety

Univariate logistic regression was used to investigate the probability of experiencing any grade or Grade 3 or higher (Gr3+) AEs for the following safety endpoints: palmar-plantar erythrodysaesthesia syndrome (PPES), hypertension, myalgia, diarrhoea, and hyperbilirubinemia or increased blood bilirubin. With the exception of Gr3+ hypertension, there very few occurrences of Gr3+ AEs (rates $\leq$ 2.2%).

The only slopes with p-values <0.05 were those for any grade myalgia and any grade PPES versus ripretinib exposure (p = 0.0057 and 0.0023, respectively). The slopes for these 2 endpoints were relatively shallow. The probability of AE occurrence increased only from 27.5% to 64.1% for any grade myalgia and from 20.1% to 60.9% for any grade PPES over the large range of average ripretinib Cmin up to time of event/end of treatment for both safety endpoints. Exposures ranged from ripretinib Cmin of 31.2 ng/mL to the 46-fold higher ripretinib Cmin of 1450 ng/mL.

Efficacy

Observed combined molecular weight-adjusted ripretinib + DP-5439 Cmin up to the time of disease progression/death or up to the time of censoring was used as the exposure measure for the analysis and was divided into 4 equally sized, rank-ordered, exposure groups [values ≤ first quartile (Q1) to values > third quartile (Q4)] for the exposure-PFS analysis, as seen in Figure 5.

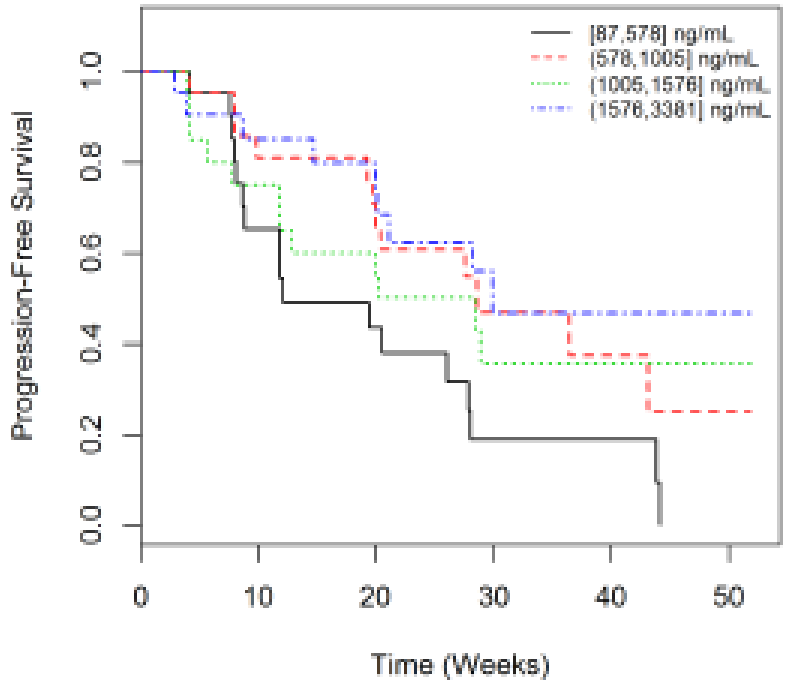


Figure 5: Kaplan-Meier Plots for PFS by active moiety exposure group

PFS was analysed as a time-to-event variable using the Cox proportional hazard model. The following baseline covariates were tested but found non-significant: age, race, body weight, ECOG performance status, number of prior anticancer treatments, mutation status (4 categories, namely, 1: KIT exon 9, 2: KIT exon 11, 3: KIT/PDGFRα wild type, and 4: PDGFRα and KIT other exons). The appropriateness of the Cox proportional hazard models for PFS was primarily assessed through goodness-of-fit plots. Model diagnostics included plots of Schoenfeld residuals versus time.

The HRs and 95% CIs for combined Cmin Q2 to Q4 relative to Q1 are depicted in Figure 6. All HRs for combined Cmin Q2 to Q4 were <1, indicating improved PFS compared to Q1. Only the HR for combined Cmin Q4 was statistically significant (95% confidence interval = 0.39 [0.17, 0.89]; p = 0.025).

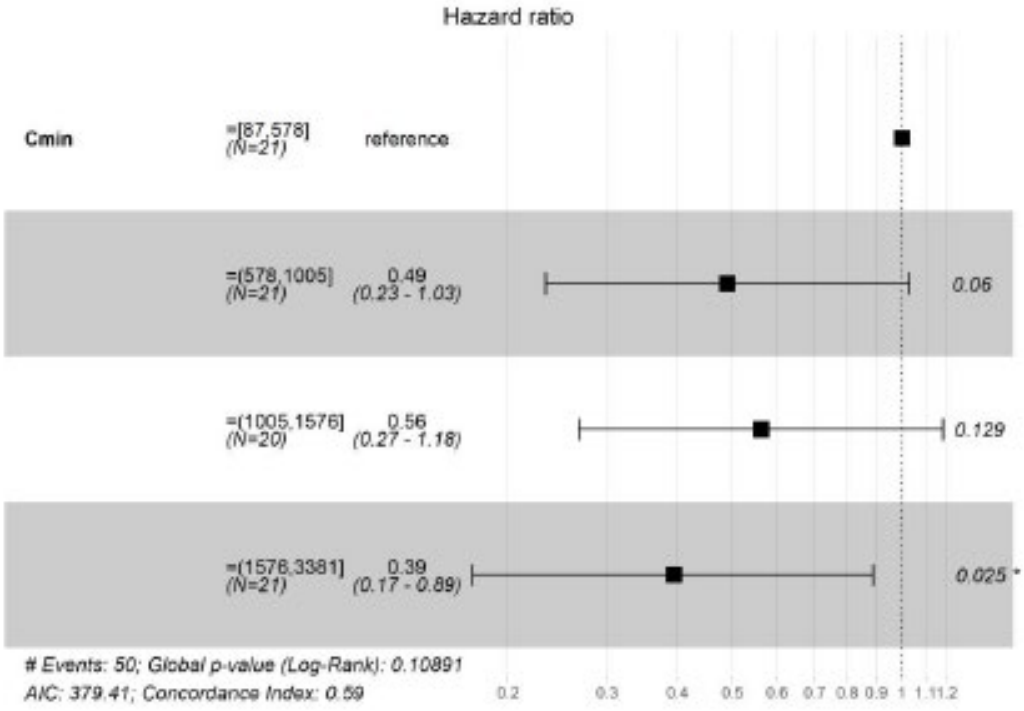


Figure 6: Hazard ratios and 95% CI for the final PFS exposure model by active moiety exposure group. Square symbol and error bars represent HRs and associated 95% CIs, respectively. HRs are presented from top to bottom for exposure groupsQ1 (reference), Q2, Q3, and Q4.

2.4.4. Discussion on clinical pharmacology

Methods

Bioanalysis

The bioanalytical methods were adequately validated. The lack of cross-validation was accepted since the Pop-PK analysis was based on the data supported by the same bioanalytical method.

Pharmacokinetic data analysis

The standard methodology of the pop PK analysis is accepted. Overall, VPCs and pcVPCs showed the model seemed to describe the data adequately.

The structural population PK model incorporates a two-compartment model with a sequential zero- and first-order absorption process and linear elimination. A dose-dependent decrease in the relative bioavailability (Frel) with increasing dose, a dose-independent food effect on the duration of zero-order drug release, and a dose-dependent food effect on Frel were incorporated. The incorporation of dose and food effects on bioavailability is purely empirical. As it seems to be highly correlated, this increases the difficulty of the model interpretation. A reduced bioavailability as dose increases could be explained by the reduced solubility of ripretinib within the gastrointestinal tract. The increase in the relative bioavailability as dose increases in the presence of high fat meal conditions might reinforce the justification of higher solubility in the presence of surfactants. Overall, the proposed model properly characterizes the observations, although it lacks to mechanistically explain the absorption process.

A significant model misspecification based on the GOF was observed at higher concentration values, indicating a likely bias in the Cmax characterization. It is agreed that the model misspecification is

partially unclear since pc-VPC does not show any significant bias around Cmax and the additional difficulty to experimentally capture the Cmax. Since no experimental predicted concentrations were considered for the exposure-response analysis, such difference in the GOF plots should be considered of minimum relevance.

Variability on Vp/F is very high (1465%) and it cannot be attributed to particular covariates and denotes instability in the model. The condition number is high, indicating that the model is over parametrised. The VPCs and further diagnostic plots show however that the model is nevertheless able to describe the data. The role of this model in this application is primarily the description of the data, and support of dosing recommendations in special populations. Overall, the model is not considered pivotal for the application, and an update was not be requested. The significance of the covariates retained in the model should however be interpreted with caution, due to the issues cited above.

Replacing the covariate sex by body weight on CL/F lead to a statistically inferior model, which is agreed.

The management of metabolite concentrations in the model is adequate. VPCs indicate that the metabolite model is able to describe DP-5439 data. No covariate analysis was performed for the DP-5439 model. Since the PK of DP-5439 is relatively similar to ripretinib (ie similar elimination and excretions pathways, similar half-life), the DP-5439 is directly impacted by the covariates from the ripretinib model, and this may be sufficient.

Overall, variability in all parameters is high, and the confidence intervals are overlapping with the reference patient (male, fasted, without gastrectomy), indicating the covariates likely do not have a clinically relevant impact.

Absorption

Study DCC-2618-01-001

The metabolite to parent ratio increased from single dose to steady state, with AUC0-t ratios of 0.49 at single dose and 1.29 at C1D15 of 150 mg QD administration. This is in line with the slightly longer t1/2 of DP-5439.

For the selection of the dose for the phase 2 part of study DCC-2618-01-001, a threshold in active moiety AUC0-24 was selected based on preclinical studies. The applicant claims that >90% of the patients would have an exposure above this threshold when administered 150 mg ripretinib QD. While no analysis has been provided to support this claim, single dose data indicates that mean AUC0-24 is higher than 10000 when considering both ripretinib and DP-5439, this issue will thus not be pursued.

The administration of 150 mg ripretinib with a high-fat meal increased the exposures (AUC_{0-24}) to ripretinib and the metabolite DP-5439 by approximately 30% and 47%, respectively, compared to the fasted condition. The fasted condition corresponded to a short fast, and not an overnight fast as in some of the other studies. The effect may thus be slightly underestimated. Since ripretinib was then administered regardless of food intake, including in the phase 3 study, this recommendation is agreed. Of note, the magnitude of the effect is smaller than upon co-administration with itraconazole.

The food effect differed depending on the administered dose. It was negligible for 100 mg ripretinib, which will be used in case of dose reduction due to adverse events.

While the food effect may not be clinically relevant, its effect on PK is nonetheless significant, thus dose proportionality analyses were stratified by feeding status.

Study DCC-2618-01-002

The design of the bioequivalence study DCC-2618-01-002 was adequate, including the wash-out time of at least 7 days and the fasted state. Since only one strength (50 mg) is available and given the adverse events observed in healthy subjects, it is acceptable to study 50 mg.

Some batches of drug substance were milled, while others were not in the clinical process batches. Since the batch selected as reference contained unmilled substance, this is considered to constitute an extreme which is compared to the test formulation containing milled substance. Since these two formulations were demonstrated bioequivalent, the bioequivalence is acceptable for the whole range of clinical process batches.

The intended commercial formulation (test formulation) and the formulation used during clinical development in Phase 1 Study DCC-2618-01-001 and Phase 3 Study DCC-2618-03-001, were demonstrated to be bioequivalent for ripretinib. There is no requirement of equivalence on DP-5439. Its concentration was however similar between the reference and test formulation.

PK parameters from this study are used in the SmPC and for safety calculations.

Distribution

The in vitro protein binding to human serum albumin (HSA) and α-1 acid glycoprotein (α-1-AGP) and blood distribution studies with ^{14}C-ripretinib were conducted in adequate conditions. The studied concentration range covered the expected physiological concentrations upon 150 mg QD dosing of ripretinib.

Both ripretinib and its active metabolite DP-5439 bind to plasma proteins at > 99% and ripretinib primarily partitions to plasma. There was no concentration dependency for binding of ripretinib or DP-5439 to HSA. A slight concentration dependency in the binding to α1-AGP is noted for both ripretinib and DP-5439. Even though the absolute difference appears small, this may represent a ca 4-fold increase in free active moiety. The applicant committed to measuring free concentration in the planned hepatic impairment study. (See post authorisation measures section).

The blood distribution of DP-5439 was not investigated and its protein binding was not determined in human plasma, but only in solutions of HAS or α-1-AGP. A cellular distribution similar to ripretinib is assumed and therefore the lack of blood distribution data for DP-5439 is acceptable. Regarding protein binding, the data with human serum protein is in the same range as ripretinib, therefore similar overall protein binding in human plasma is expected. The SmPC claim "*Both ripretinib and its active metabolite DP-5439 bind to plasma proteins at ≥ 99%."* is considered acceptable.

Elimination

The applicant presented a detailed discussion of the formulation challenges that prevented the execution of a mass balance study in human. It is agreed that such a study is not feasible at the moment. In Q4 of the central advice EMA/CHMP/SAWP/132691/2020, a thorough justification was demanded regarding the formulation challenges, and the applicant complied with this request. The advice further asked the applicant to consider an iv microdosing study to obtain information about the volume of distribution and clearance. This information is however not considered essential for this MAA and a microdosing study is therefore not requested.

In question 4b, the applicant also inquired about the extent of characterisation of ripretinib metabolism and excretion, which was considered sufficient with comments on the stability of glucuronides in samples, severe renal impairment, hepatic impairment studies and potential interactions in the advice. Both issues were adequately addressed by the applicant in the MAA, with planned studies where data is not currently available.

In the absence of mass balance study, the applicant collected data from non-labelled ripretinib. The overall recovery of ripretinib and DP-5439 at 168h is 40.3%. Considering the t1/2 of both ripretinib and DP-5439 in plasma, both should be fully eliminated within 168h, which is also suggested by the plateau in recovery. A longer study would thus not necessarily provide more information. It is known that quantitative extraction of unlabelled compound from faeces is challenging and may contribute to the low recovery.

Urine and plasma samples were also analysed to detect further metabolites (see section below). 3 metabolites were identified in plasma, which contributed each to less than 1% of the total peak area.

In urine, four additional metabolites were identified. Considering the total peak area through 168 hours postdose, ripretinib accounted for 15 to 100%, DP-5439, hydroxy-DP-5439-1 (M1), DP-5439-glucuronide (M24), DCC-2618-glucuronide (M27) and Oxy-DP-5439-2 (M23) ranged from 19 to 30%, 6 to 23%, 4 to 29%, 9 to 35%, and 2 to 6% (in 48h) of the total peak area, respectively. Even considering the lowest fractions of ripretinib and DP-5439, (15% and 19%), these semi-quantitative measures indicate that the remaining metabolites would presumably not significantly impact the overall recovery of ripretinib.

Overall, the available data, both in vivo and in vitro indicates that the PK of ripretinib and its metabolites is similar in preclinical species and in human, suggesting that indeed, the low recovery is simply due to the sensitivity of methods when using unlabelled material, and that the risk of identifying additional major metabolites is low. It could however not be assured that all metabolites are detected and there is a risk that minor metabolites are missed since unlabelled material is used. This is considered acceptable, as ripretinib is intended for use in advanced malignancies, metabolite qualification is not a formal requirement (ICH S9 Q&A). Consequently, the excretion of ripretinib is considered adequately described. The applicant provided pre-clinical data suggesting no significant ripretinib accumulation in a particular tissue/organ and reviewed safety information of studies DCC-2618-01-001 and DCC-2618-03-001 finding no particular safety concerns in melanin-containing tissues. As the recovery curve of non-labelled ripretinib and DP-5439 reached a plateau by 1-week of collections (168 h) and the elimination t1/2 of both moieties indicate that ripretinib and DP-5439 should be fully eliminated by this time, it is consistent to state that accumulation of ripretinib in other tissues/organs is not expected to be clinically relevant.

The reaction phenotyping indicated that CYP3A4/5 was the major pathway in the metabolism of ripretinib. In addition, CYP2C8 and CYP2D6 also play a role in the metabolism of ripretinib. This is consistent with the SmPC claims.

An in vivo interaction study with itraconazole and a study with rifampicin were conducted, see in the interaction section. The applicant compared the magnitude of effect of CYP3A4 inhibition or induction, where the co-administration of the strong CYP3A4 and PgP inhibitor itraconazole lead to AUC0-∞ increase by 99% for both ripretinib and DP-5439, without the need for a dose adjustment. Consequently, it is agreed that an interaction with CYP2C8 or CYP2D6 inhibitors is likely to be of lower magnitude. This is also supported by the data on CYP2D6 polymorphism.

No clear trend was visible in AUC0-24 of Cmax of ripretinib and DP-5439 when stratified by CYP2D6 phenotype. Any trend may be masked by the overall high variability in the PK of ripretinib, and that few patients were poor metabolisers. Nevertheless, the lack of trend supports that CYP2D6 has a minor role in the metabolism of ripretinib and that CYP2D6 polymorphism is expected to have a minor impact on the PK of ripretinib and DP-5439.

The reaction phenotyping indicated that CYP3A4 was the major pathway in the metabolism of DP-5439. In addition, CYP1A2, CYP2E1, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 each may also play a role in the metabolism of DP-5439.

DP-5439 is the only major metabolite currently identified in plasma. The other detected metabolites are minor metabolites and do not require qualification in preclinical species or in vitro DDI studies.

The probability that major metabolites remain unidentified in urine and plasma is deemed low. There is a risk that minor metabolites are missed since unlabelled material was used in vivo.

Dose proportionality

Fasted state: Despite the substantial variability, the PK of both ripretinib and DP-5439 appears less than dose proportional across the dose range 20-250 mg, for Cmax, AUC_{0-24} (or AUC_{0-12}) at C1D1. The difference appears less striking at C1D15, this may however be masked by using AUC_{0-12}, as 24h is not available. As noted earlier, AUC_{0-12} is not considered appropriate for a substance with a half-life of 12.6h and 15.6h for ripretinib and DP-5439, respectively.

Time dependency

The available data seem to indicate substantial accumulation, these are however misleading as they are based on AUC0-12, which is not adequate for ripretinib and DP-5439, which have longer t1/2 and tmax ranging from 2-24h for ripretinib and 4-25h for DP-5439. Trough concentrations and the pop PK analysis may provide a better base for conclusions on time-dependency in this case. The accumulation of ripretinib and DP-5439 in the expansion phase is nevertheless in the expected range for a compound with a half-life of 12.6h and 15.6h, respectively, indicating no evidence of time dependency.

The applicant´s conclusion that there was no evidence in time dependency based on trough concentrations is agreed.

Intra- and inter-individual variability

Inter- and intraindividual variability was high to very high on all parameters, despite the precision of their estimates.

Pharmacokinetics in target population

See pop PK analysis.

The applicant discussed the therapeutic window for ripretinib, DP-5439 and the active moiety. A two fold exposure was reached in patients given 150 mg BID (upon disease progression). At this exposure, adverse events were increased. The upper limit of tolerated exposure of 2 fold exposure of both ripretinib and DP-5439 was not agreed and dose adjustments were requested. The applicant presented a new analysis of safety in these patients, and it is now agreed that doubled PK exposure resulting from dose escalation to ripretinib 150 mg BID was generally well tolerated. The largest difference was observed for abdominal pain and anaemia, and it is agreed that it is not possible to truly distinguish whether the difference is due to disease progression or is a true ADR.

Warnings are in place for patients at risk of reaching a twofold exposure, namely patients with moderate and severe hepatic impairment (close monitoring, SmPC section 4.2), patients receiving strong CYP3A4/PgP inhibitors (caution and monitoring, SmPC section 4.4 and 4.5), which is deemed adequate. A similar warning is also requested for patients who need co-administration with strong CYP3A4 inducers and thus require 150 mg ripretinib BID (see below).

Special populations

Impaired renal function

It is agreed that no dose adjustment of ripretinib is necessary for subjects with mild or moderate renal impairment, and that no recommendation can be made for severe renal impairment. This is consistent with the SmPC claims. The data from the new cohort confirmed the conclusions from the pop PK.

Impaired hepatic function

Since both ripretinib and DP-5439 are metabolised, and in the absence of mass balance study, a dedicated hepatic impairment study in patients with moderate to severe HI is warranted. The applicant committed to present the data of the ongoing study DCC-2618-01-004 and to include the unbound fraction in the investigations. The data is expected in Q1 2022.

The design and dose of study DCC-2618-01-004 are considered adequate.

Based on the pop PK data, it is agreed that no dose adjustment in mild hepatic impairment is required.

Gender & Weight

Gender is a significant covariate on CL/F in the pop PK model for ripretinib. The increased exposure in females is however not clinically relevant.

Race & Age

Age has been shown to have no effect on the PK of ripretinib and DP-5439.

No clinically relevant changes in exposure were observed in patients according to their race status.

Interactions

The table below summarises the in vitro findings and their consequences for interactions with ripretinib and DP-5439 as victim and perpetrator.

DDI summary for ripretinib and DP-5439 (in vitro data unless noted otherwise)

Enzyme/ transporter	Perpetrator	Victim	Consequence
CYP1A2	No inhibition, no TDI, mRNA downregulation	No	SmPC warning for downregulation by ripretinib
CYP2B6	No inhibition, no TDI, induction by ripretinib and potentially DP-5439	No	SmPC recommendation for induction
CYP2C8	Inhibition by both, no TDI, no induction data	Ripretinib is substrate, minor pathway	In vivo study with 2C8 substrate planned. SmPC warning for NTI substrates
CYP2C9	In vitro inhibition excluded by mechanistic static modelling, , no TDI, no induction data	No	-
CYP2C19	In vitro inhibition excluded by mechanistic static modelling,, no TDI, no induction data	No	-
CYP2D6	No inhibition, no TDI	Ripretinib is substrate, minor pathway	-
CYP3A4	No direct systemic inhibition, direct inhibition not excluded in the	Major pathway for both	Caution for co-administration with strong inhibitors; dose adjustment with inducers;

	intestine, MBI by ripretinib (intestine), induction by both	In vivo AUCR with itraconazole: 202% for the active moiety. In vivo AUCR with rifampicin: 40% for the active moiety. Dose adjustment to 150 mg BID with strong inducers	SmPC recommendation for co-administration with CYP3A4 substrates that are mostly metabolised in the intestine; SmPC warning for induction; warning in SmPC 4.4 & 4.5 to add a barrier methods when using contraceptive steroids (teratogen); **in vivo study with midazolam for induction & inhibition in the intestine**
PgP	Inhibition in the intestine by ripretinib, not by DP-5439	Ripretinib & DP-5439 are substrates, in vivo AUCR with itraconazole 202% for the active moiety.	SmPC warning (perpetrator). Caution for co-administration with strong inhibitors.
BCRP	Inhibition by ripretinib (systemic and intestine) and DP-5439	DP-5439 is substrate, ripretinib data inconclusive	New in vitro BCRP substrate study with ripretinib Actionable SmPC recommendation for both perpetrator and victim interactions.
OATP1B1	No	No	-
OATP1B3	No	No	-
OAT1	No	No (DP-5439 only)	-
OAT3	No	No	-
OCT1	*No (ripretinib only)*	*No (ripretinib only)*	-
OCT2	No	No	-
BSEP	*No*	*No (DP-5439 only)*	-
MATE1	*Inhibition by DP-5439, not ripretinib*	*No*	Actionable SmPC recommendation (perpetrator)
MATE2-K	*No*	*No*	-

Italic denotes non mandatory transporters.

Victim interactions

The in vivo inhibition of CYP3A4 and PgP by itraconazole results in a significant AUCR, though without alteration to the metabolite/parent ratio a both ripretinib and DP-5439 are CYP3A4 and PgP substrates. The applicant recommends caution and monitoring when co-administering strong CYP3A4 inhibitors. A similar warning for PgP has been included. Information that ripretinib and DP-5439 are PgP substrates has been included in the SmPC.

The applicant proposed a warning text for grapefruit juice, as part of aligning the PIL and the SmPC. The content of the warning is not agreed. Grapefruit is not a necessary part of a medical treatment and requiring monitoring along with grapefruit juice is an exaggerated measure and avoiding grapefruit juice is considered an easier measure to implement. Grapefruit may be mentioned after the other CYP inhibitors: *ingestion of grapefruit juice is not recommended*. The applicant accepted the proposed text.

Co-administration with the strong CYP3A4 inducer rifampicin (study DCC-2618-01-006) resulted in a 40% AUCR, as compared to ripretinib given alone. A dose adjustment to 150 mg BID is proposed, if co-administration with a strong CYP3A4 inducer is necessary. This is agreed for strong inducers, on the basis that 150mg ripretinib BID has been demonstrated to achieve approximately a two-fold exposure compared to 150mg ripretinib QD. The ripretinib dosing frequency is to be increased during the co-administration period with the inducer.

A similar dose adjustment is proposed for moderate CYP3A4 inducers and is based on PBPK modelling. The modelling for moderate inducers cannot be accepted, as doubts are raised on the predicted extent of induction with the CYP3A4 moderate inducer efavirenz, and the efavirenz compound file has numerous flaws. The simulated data should not be included in the SmPC. The applicant accepted to remove the PBPK data.

The potential loss of efficacy in patients requiring co-administration with a moderate CYP3A4 inducer still needs to be addressed, and a dose adjustment may still be required but an exact recommendation cannot be made at this point. As a cautionary measure, close monitoring for both efficacy and safety should be considered if the dosing frequency was increased. The applicant accepted the proposed text.

Dose adjustments are cross-referenced in section 4.2 and 4.4.

Concomitant administration of pantoprazole 40 mg QD did not affect exposure to ripretinib. Ripretinib AUC0-t, AUC0–∞, and Cmax values met the bioequivalence criteria when co-administered with pantoprazole. The AUC of DP-5439 was slightly more elevated. Since the study may not be sufficiently powered for this endpoint, the issue is not pursued. It is agreed that the impact of co-administration of pantoprazole, and by extension other gastric acid modifying agents is not clinically relevant.

The applicant concludes that ripretinib is a weak substrate of BCRP at 10 µM which is supraphysiological and where BCRP may be saturated. Since data is missing in the relevant physiological concentration range, a new in vitro experiment is required for BCRP, which follows the design outlined in appendix 3 of the DDI GL. The applicant committed to performing this study post marketing and included a warning in the SmPC (See post authorisation measures section-REC).

Perpetrator interactions

DP-5439 is a major active metabolite and its interaction potential was studied along with ripretinib. The relevant cutoffs are listed in the table below:

Substance	Fraction unbound [%]	Cmax [µM]	50x Cmax,u [µM]	25xInlet Cmax,u [µM]	0.1xDose/250 ml [µM]
ripretinib	1	1.5	0.75	1.56	117,7
DP-5439	1	1.6	0.81	na	na
Data from study DCC-2618-01-001 C1D15, ripretinib 150 mg QD, ripretinib 761 ng/mL, DP-5439 804 ng/mL, ka 0.0015 min^{-1} from pop PK					

All mandatory CYPs and transporters were studied, including CYP3A4 with midazolam and testosterone, and time dependant inhibition for CYPs. Ki was not determined, but as experiments were performed at substrate concentrations at Km, it can be assumed that Ki = IC50/2. The design of in vitro assays was generally acceptable.

A second set of Ki values for CYP2C19 and 2C19 inhibition by ripretinib and DP-5439 was provided, and mechanistic static modelling with the lowest value confirmed the lack of relevant interaction at physiological concentrations.

For CYP2C8, the recommendation has been updated with more actionable measures and examples, until in vivo data become available. The applicant committed to reporting the results of DCC-2618-01-007 (with repaglinide), and results are expected in March 2023. (See post authorisation measures section-REC)

Studying in vitro inhibition of CYP3A4 by ripretinib up to 118 µM was not feasible due to the limited solubility of ripretinib. Inhibition in the intestine cannot be excluded and may result in a clinically relevant interaction with substrates of CYP3A4 that are mostly metabolised in the intestine. The applicant attempted modelling the interaction, which was not accepted. The applicant accepted the proposed SmPC text and in vivo study (see below, induction).

Regarding the TDI of CYP3A4 by ripretinib, the applicant´s conclusion that it lacks clinical relevance is still not agreed. The applicant was invited to discuss the clinical relevance of this interaction in the intestine, particularly since the absorption of ripretinib is slow (tmax 4h). Since the interaction is complex (induction, metabolism-based inhibition in the intestine, partially irreversible, and potential direct inhibition in the intestine), PBPK modelling proposed by the applicant is not deemed appropriate to exclude to clinical relevance of this interaction. Therefore, a multiple dose in vivo study with midazolam is deemed necessary to exclude interactions in the intestine and systemically for the induction aspect. Until data is provided to exclude an interaction, a recommendation should be included in SmPC section 4.5. The applicant accepted the proposed SmPC text and committed to perform a multiple dose interaction study with midazolam. (post authorisation measures section-REC)

A new CYP induction study was provided for ripretinib. The applicant´s conclusions that ripretinib and DP-5439 do not induce CYP 2B6 and 3A4 are not agreed, as signals were seen in the new study for ripretinib, confirming the earlier potential signals.

A multiple dose in vivo CYP3A4 induction study with midazolam is thus warranted and should be submitted post authorisation. As DP-5439 is driving a part of the interaction, its PK characteristics should be taken into account in the design of the study. Furthermore, the study should include aspects of CYP3A4 inhibition in the intestine. Until the results become available, warnings for potential loss of efficacy of sensitive CYP3A4 substrates should be included in the SmPC, and a warning for potentially clinically relevant interaction with substrates of CYP3A4 that are mostly metabolised in the intestine. The applicant accepted the proposed SmPC text and committed to perform a multiple dose interaction study with midazolam. (post authorisation measures section-REC).

As sensitive substrates of CYP2B6 are infrequently used, an SmPC warning for loss of efficacy of sensitive CYP2B6 substrates is considered a sufficient risk management measure and no in vivo study is requested. The applicant accepted the proposed text.

In the CYP1A2 induction assays, concentration dependant down-regulation of CYP1A2 was apparent at non-cytotoxic concentration. As this effect is seen in the data of both ripretinib and DP-5439, this should be followed up in vivo. Considering that NTI CYP1A2 substrates are infrequently used, an SmPC warning is considered a sufficient risk management measure. The applicant accepted the proposed text.

Ripretinib is teratogen, and as such an in vivo study regarding its effects on contraceptive steroids should be performed regardless of the in vitro induction results if the drug is intended for use in fertile women, as is the case here. The applicant argued that the sought indication includes predominantly patients beyond the typical age of child-bearing potential. It is also agreed that a study in healthy subjects is not feasible, as steady-state concentrations would be required, which were not safe in healthy subjects. The suggested measure of including advice in SmPC section 4.4 (to add a barrier method if systemic contraceptive steroids are used) is adequate, with the addition of a similar warning in section 4.5.

In the future, should ripretinib be used in other indications including women of childbearing potential, the feasibility of an interaction study in patients should be re-evaluated.

Ripretinib is an inhibitor of BCRP at concentrations relevant in the gut and the liver. The applicant included actionable recommendations for co-administration with BCRP substrates and examples in the SmPC.

An actionable recommendation was proposed for the inhibition of PgP by ripretinib and is agreed.

In vivo inhibition of MATE-1 by DP-5439 cannot be excluded based on the in vitro data. The applicant included actionable recommendations for co-administration with BCRP substrates and examples in the SmPC.

Ripretinib inhibited OATP1B3 with 40% at the highest concentration of 3 µM, which is below the inlet cutoff of 6.6 µM, calculated with ka 0.1 min^{-1}. The applicant argued that a ka of 0.0015 min^{-1} (from the pop PK analysis) was more relevant than the worst case scenario. This is agreed. The inhibition of OATP1B3 can thus be excluded with the new cutoff of 1.56 µM.

In the future, should a dose of 150 mg ripretinib bid be claimed in case of disease progression, then the following data would be used to determine the cutoffs: study DCC-2618-01-001 C1D15, ripretinib 150 mg BID, ripretinib 1290 ng/mL, DP-5439 1800 ng/mL. This would correspond to a 50xCmax,u of 1.26 µM for ripretinib and 1.81 µM for DP-5439. The inlet cutoff for ripretinib would then be 1.56 µM and the intestinal cutoff would remain unchanged. This entails that, in addition to known interaction that may increase in magnitude, perpetrator interactions on CYP2D6, 2C9 and 2C19 should be re-assessed if 150 mg BID was to be given.

Exposure relevant for safety evaluation

The applicant initially used AUC0-12 in their preclinical assessment, which was not agreed, particularly considering the t1/2 of both ripretinib and DP-5439. The use of data from AUC0-∞ values obtained from healthy participants in the DCC-2618-01-002 study who received single-doses of ripretinib 150 mg. This is agreed as in the absence of time-dependency, AUCinf upon single dose should be representative for AUCtau at steady state.

The choice of Cmax,ss used in the preclinical assessment is agreed.

Exposure/response

A supratherapeutic concentration range was included in the QTc study, which is adequate. It seems like a linear model cannot describe the exposure/QTc relationship, in particular for DP-5439. Nevertheless, both the raw data and the model do not indicate a prolonged QT interval. Both the ripretinib and DP-5439 QTc relationship indicated a shorter QTc.

Observed average Cmin has been used in exposure response analyses instead Cmax, which is often relevant for safety. The sampling in the studies (mostly in the phase 3 study) is not sufficient to estimate Cmax. Pop PK predictions may have been used for the analysis instead. However, Cmin is expected to correlate with AUC and Cmax, and as such the analysis may be adequate.

Ripretinib and DP-5439 are equipotent, therefore a correction for potency is not required in the combined exposure calculation. The difference in molecular weight between them is small, therefore it would have been acceptable not to correct for it. Overall, the calculation of the combined exposure is acceptable.

The exposure/safety modelling approach is deemed adequate. The only identified correlations were between average ripretinib Cmin up to the time of the first AE occurrence or end of treatment and the AEs of any grade myalgia and any grade PPES. The range covering the majority of exposure at the proposed dosing regimen showed a probability of any grade Myalgia and any grade PPES from 33 to 45% and 29 to 40%, indicating minimal impact in terms of safety due to ripretinib.

The exposure/efficacy modelling approach was adequate. Since the modelling is based on patients that were all randomized to 150 mg one should interpret the E-R relationship with caution. It is difficult to discriminate between the effect of exposure and other reasons as only one dose was administered in the dataset. As such a confounded relationship cannot be excluded.

A positive exposure-response relationship between active moiety Cmin up to the PFS was observed, with lower hazard ratio and improved PFS in exposure groups Q2 to Q4 relative to Q1. The lack of a clear and definitive exposure-efficacy relationship might be undermine by the large variability, but additional efforts should be performed in order to understand the exposure-efficacy relationship. In this sense, the applicant was encouraged to evaluate other exposure metrics (AUC or Cmax for the active moiety) related to PFS. The applicant justified the absence of evaluation of alternative PK metrics due to the higher eta-shrinkage, which may compromise the individual value predicted, which is accepted. The adequacy of Cmin to explain the exposure-response relationship is endorsed. The applicant clarified the lack of evaluation of unbound plasma concentrations in DCC-2618-03-001 study. Unbound ripretinib and DP-5439 observations will be collected in DCC-2618-01-004 study, which is endorsed.

2.4.5. Conclusions on clinical pharmacology

The PK of ripretinib and its major active metabolite DP-5439 has been generally well-described. From a clinical pharmacology point of view, ripretinib is approvable, as the applicant has committed to the list of recommendations and accepted the suggested SmPC warnings.

Description of post-authorisation measure(s)
1. Study DCC-2618-01-004 (hepatic impairment). Unbound PK at Cmax and 24h, 40 patients– June 2022-MEA
2. New in vitro experiment to study whether ripretinib is a substrate of BCRP, which follows the design outlined in appendix 3 of the DDI GL– October 2021-REC
3. Study DCC-2618-01-007 (repaglinide drug interaction)– March 2023-REC
4. Multiple dose study with midazolam for systemic induction and intestinal inhibition by ripretinib and DP-5439 -*June 2025-REC*
5. ERA: Experimentally determined LogKow – March 2022-REC

2.5. Clinical efficacy

Ripretinib was developed as a pan-KIT and PDGFRA inhibitor with the capacity to broadly inhibit KIT and PDGFRA kinase activity, including wild type as well as primary and secondary mutations.

This application is based on two clinical studies, in support of ripretinib for the treatment of patients with GIST. A phase 1 study, DCC-2618-01-001, (data extracted at the data cut-off date; 01 Mar 2019) which an ongoing dose escalation/dose expansion (FIH) study and the Phase 3 Study DCC-2618-03-001 (INVICTUS) for which enrolment is completed and with data cut-off 31 May 2019 (data extracted at the data cut-off date) presenting the results for the primary analysis.

The currently proposed indication is:

Qinlock is indicated for the treatment of adult patients with advanced gastrointestinal stromal tumour (GIST) who have received prior treatment with three or more kinase inhibitors, including imatinib.

Assessment of the efficacy of ripretinib will be based on two studies, the Dose-Response study DCC-2618-01-001 and the Phase 3, pivotal study DCC-2618-03-001, presented separately.

An additional Phase 3 study, DCC-2618-03-002 (INTRIGUE), will evaluate the efficacy, safety, and quality of life (QoL) of ripretinib versus (vs.) sunitinib in second line GIST.

Overview of Clinical Studies with Ripretinib Assessing Efficacy

Study	Study Design Objectivesa	Population (age) Schedule of administration	Study groups	Number of subjects
DCC-2618-01-001	Open-label Phase 1 study, with two phases (escalation phase and expansion phase). **Escalation phase** Primary Objectives: • To determine the safety and tolerability of oral ripretinib • To determine the MTD and RP2D of oral ripretinib Secondary Objectives: • To determine the PK profile of oral ripretinib • To document preliminary evidence of ripretinib anti-tumour activity in patients with advanced malignancies • To assess the effect of food on the PK profile of oral ripretinib **Expansion phase** Primary objectives: • To further evaluate the safety and tolerability of oral ripretinib • To determine the anti-tumour activity of ripretinib in all diseases under study Secondary objectives: • To determine the PK, including population PK, profile of oral ripretinib • To evaluate the safety and tolerability of the RP2D of oral ripretinib in a cohort of patients with moderate and severe renal impairment • To determine allele fraction of KIT and PDGFRA mutations in plasma cfDNA and compare it with mutation allele fraction in GIST tumour tissue and their association	Patients with histologically confirmed solid tumours or hematologic malignancies, aged ≥18 years **Treatments:** Escalation phase Sequentially increasing dose levels of oral ripretinib QD or BID in repeated 28-day cycles Expansion phase oral ripretinib dose: 150 mg QD, in repeated 28-day cycles	Escalation Phase: oral ripretinib dose: 20mg BID, 30mg BID, 50mg BID, 100mg BID, 150 mg BID, and 200mg BID, and 100mg QD, 150 mg QD, and 250mg QD Expansion phase: • 4th Line GIST • >4th Line GIST • 2nd-3rd Line GIST • Other solid tumours • Systemic mastocytosis • Malignant gliomas • Melanoma • Germ cell, penile, and non-small cell lung cancer • Renal impairment (solid tumours) • Soft tissue sarcomas For the 142 patients with GIST dosed at 150 mg QD in the Escalation and Expansion phase, the mean (SD) age was 60.4 (11.36) years.	**01 Mar 2019 cut-off** Total enrolled = 237 71 patients on treatment: • 12 patients in escalation; • 59 patients in expansion

Study	Study Design Objectivesa	Population (age) Schedule of administration	Study groups	Number of subjects
	with prior treatment and study drug response.			
DCC-2618-03-001 (INVICTUS)	2-arm, randomised, placebo-controlled, double-blind, international, multicentre study Primary objective: • To assess the efficacy (PFS) of ripretinib by IRR in patients with advanced GIST who had received prior anticancer therapies Secondary objectives: • To assess ORR by IRR • To assess other parameters of efficacy, including but not limited to TTP and OS • To assess the PK/PD relationship of ripretinib • To assess the robustness of efficacy using a sensitivity analysis • To assess improvement of disease-related symptoms and QOL • To assess the safety of ripretinib	Patients aged ≥18 years, with advanced GIST, and had received ⩾3 prior lines of treatment including imatinib, sunitinib and regorafenib. Treatments • Ripretinib 150 mg QD + best supportive care • Placebo + best supportive care • Optional ripretinib 150 mg BID for patients with disease progression after the completion of Cycle 2. Treatment administered in 28-day cycles	Double-blind period • Ripretinib • Placebo Open-label period • Ripretinib (previous placebo) • Ripretinib (previous ripretinib) Of the 129 patients in the ITT population, the mean (SD) age of the study population at informed consent was 60.1 (11.84) years. Most patients (118, [91.5%] patients) had ECOG PS ⩽1	**31 May 2019 cut-off** Double-blind period Ripretinib = 85 Placebo = 44 Total = 129 Open-label period Ripretinib (previous placebo) = 29 Ripretinib 150 mg QD (previous ripretinib 150 mg QD) = 11 Dose-escalated patients = 41 • 10 crossed over to ripretinib 150 mg QD and escalated to 150 mg BID • 31 patients received 150 mg QD in the double-blind period escalated to receive 150 mg BID

Abbreviations: GIST = Gastrointestinal stromal tumour; IRR = Independent Radiologic Review; PFS = Progression-free survival; MTD = Maximum tolerated dose; ORR = objective response rate; OS = overall survival; PK = pharmacokinetics; PD = pharmacodynamic; QD = once daily; QOL = quality of life; RP2D = Recommended Phase 2 dose; TTP = Time to tumour progression
[a]Only the primary and secondary objectives related to Module 2.7.3 are presented in this table

2.5.1.1. Dose-response study

Study DCC-2618-01-001, initiated in 2015, is phase 1, open-label study evaluating increasing doses of ripretinib (Escalation phase), administered as single-agent day 1-28 in repeated 28-day cycles. All patients had advanced malignancies, required to have received approved treatments known to provide clinical benefit prior to study entry and presenting a molecular rationale for activity. First patient enroled 12 Nov 2015. At DCO, 01 Mar 2019, the study was ongoing and continued to enrol and treat patients in the Expansion Phase to assess the clinical endpoints for all the protocol-defined disease cohorts. Interim data analyses in patients with advanced GIST from the interim clinical study report (CSR) are presented in this assessment. Following the dose-escalation phase, the dose-expansion phase included different disease cohorts including GIST, SM and other hematologic malignancies, malignant gliomas, melanomas, soft tissue sarcomas, and other solid tumour types associated with genomic alterations of KIT, PDGFR (A or B), TIE2, CSF1R, or VEGFR2. The clinical activity analyses were based on the ITT population.

Key Inclusion criteria: criteria specific to patients with GIST were a KIT or PDGFRA mutation and documented progression on or intolerability to at least 1 line of systemic anti-cancer therapy. Patients were to have an ECOG PS of 0 to 2 at screening and with at least 1 measurable lesion according to response evaluation criteria in solid tumours (RECIST) Version 1.1. Archival tumour tissue sample (if no anticancer therapy had been administered since the sample collection; otherwise, a fresh tumour tissue sample was required prior to the first dose), were to be obtained.

Key exclusion criteria: GIST patients with wild type or unknown KIT or PDGFRA status, prior anti-cancer treatments within 14 days, Class II-IV heart disease; arterial or venous thrombotic events within 6 or 3 months, respectively or prolonged QTcf interval, clinically significant co-morbidities; malabsorption syndromes; pregnant or lactating women.

As of Amendment 1 (03 SEPTEMBER 2015), patients were not required to have received all available treatment options following progression on imatinib. As of Amendment 5 (03 NOVEMBER 2017) a

clarification with respect to intra-patient dose-escalation from 150 mg QD to 150 mg BID, upon progressive disease, was included.

2.5.1.1.1. Statistical Methods

The Safety population included all patients who received any investigational product. The safety population was the primary set for analysis of safety data.

The Intent-to-Treat (ITT) population includes patients in the safety population, excluding those who only participated in the food effect portion. The clinical activity analyses were based on the ITT population.

Pharmacokinetic (PK) Population includes all patients in Safety Population who have at least one non-missing PK concentration.

Data collected in the Escalation Phase was summarized by dose initially assigned, in each disease group and in all patients. Pooled data from the Escalation Phase and Expansion Phase were analyzed in an analogous manner.

For GIST patients, additional analysis was done by line of therapy (2nd, 3rd, 4th, >4th, and ≥4th) for data collected in the Expansion Phase, and for pooled data from the Escalation and Expansion Phases in the following subgroups defined by dose initially assigned, 1) Initial dose = 150 mg QD; 2) Initial daily dose ≥ 100 mg

Descriptive statistics (mean, standard deviation, median, minimum, and maximum) were used to describe continuous variables. Discrete variables were summarized using frequencies and percentages.

As of the interim analysis, summary tabulations were presented for all safety data collected by the data cut-off date in all patients, and for efficacy data from Cycle 1 Day 1 to the first disease progression date or by the data cut-off date in GIST patients. At the interim analysis, safety data of all disease groups collected by the data cutoff date will be analyzed. Since the proposed indication is 4th line GIST for the NDA submission and the enrolment will not be completed for the other disease cohorts (other solid tumours, melanomas, soft tissue sarcomas, germ cell tumours, penile cancer, non-small cell lung cancer (NSCLC), and GIST and other solid tumours with renal impairment.) at the data cutoff date, the efficacy analysis will focus on the GIST patients.

Sample size

KIT or PDGFRA Mutant GIST cohorts:

Expansion Cohort 1: 4th Line

Up to 40 patients were to be enroled. A continuous monitoring plan was developed to halt enrolment into this cohort if the observed median PFS was lower than the assumed median PFS of 2 months. There are no approved treatment options for 4th line (or later) patients. The assumption of 2 months represented the potential benefit of re-challenge of imatinib. For logistical reasons, every 2 weeks the cumulative number of patients that were enroled into this cohort and the number of patients that progressed or died within 2 months of enrolment was calculated. Assuming that the true median PFS was 2 months, if the probability of observing the number of patients that progressed or died within 2 months of enrolment (or more) out of the cumulative number of patients that were enroled is less than 0.05, then enrolment into the cohort was to be halted since the true median PFS was likely less than the hypothesized 2 months. Patients already enroled continued to be treated and followed per protocol.

Expansion Cohort 2: >4th Line

Up to 35 patients were to be enroled. A monitoring plan similar to the one developed for Expansion Cohort 1 was used with the same assumptions for median PFS and duration of enrolment. The operating characteristics for this scheme were similar to those for Expansion Cohort 1.

Expansion Cohort 3: 2nd and 3rd Lines

Up to 55 patients were to be enroled into this cohort, at least 25 of these patients should have been second line patients. A monitoring plan similar to the one developed for the previous 2 cohorts was used. Based on the assumption that the majority of enroled patients represented third line patients, the hypothesized median PFS in this cohort was 3.5 months and the duration of enrolment was 8 months.

Changes in the Planned Analyses

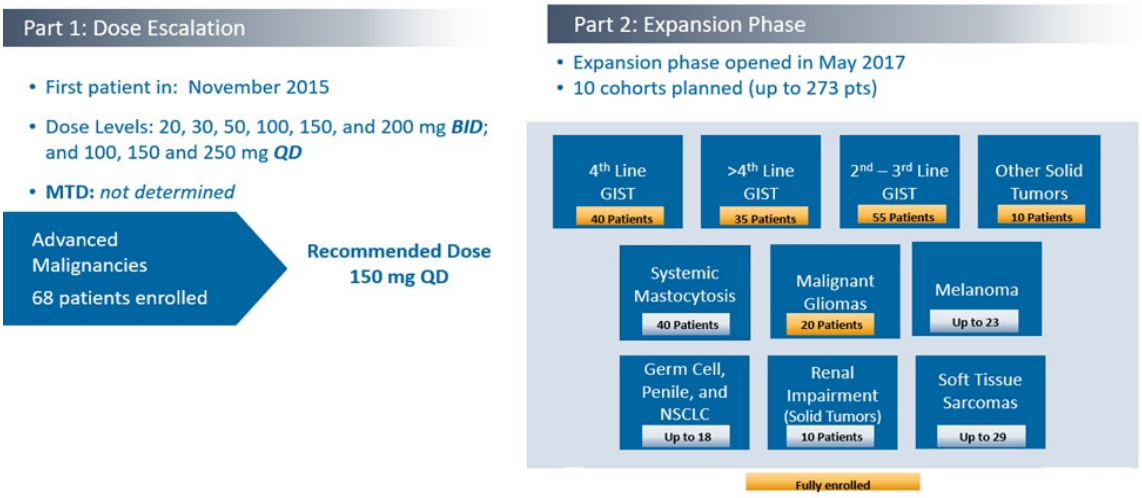
There were some changes from the planned analysis in the protocol, these were the ITT Population was defined to replace the Per-Protocol population as the main analysis set for the clinical activity of the study drug, disease control rate was reported at additional time points, the endpoint "time to best response" was changed to "time to response," a commonly used nomenclature in oncology clinical trials, an interim analysis was conducted to support the New Drug Application of the study drug in GIST patients.

The protocol has evolved over time with several amendments and the statistical analysis plan was finalized after the data cut-off for the interim analysis the submission is based on. The statistical analysis plan version 3 is dated 30 May 2019, the main change from the brief statistical analysis plan in the study protocol is the analysis population for efficacy data which is changed from a per protocol to an ITT population including all treated patients. This analysis population is considered the most relevant and the change is supported.

The interim analysis to support filing had a data cut-off of March 1, 2019. It is not clear when the timing of the interim analysis was decided and where documented. In last protocol amendment (v.7, 20 Dec 2018) it is stated that data cuts will be made, and interim efficacy and safety data will be summarized to support clinical presentations and potential regulatory submissions. Whilst the lack of pre-specification can cause concerns this study does not play the role of a pivotal study.

2.5.1.1.2. Results

Study DCC-2618-01-001 Overview



Part 1 Dose-escalation Phase

The study was initiated in 2015. Patients received ripretinib QD in 28-day cycles. A 3+3 dose escalation design was used and doses from 20 mg to 200 mg BID and 100, 150 and 250 mg QD were evaluated.

The selection ripretinib of dose, for the expansion phase, of 150 mg QD, was based on in vivo and in vitro pharmacology studies. 150 mg QD was predicted to maintain the PK exposure above the presumed threshold for efficacy in >90% of patients. Ripretinib single-dose PK parameters derived from non-compartmental 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. DP-5439 exposure generally increased as dose increased, but the increase appeared to be less than dose proportional. Furthermore, safety data during the Escalation Phase displayed three dose-limiting toxicities (DLTs), including Grade 3 lipase increased (n=2) and Grade 4 creatine kinase increased (n=1). No maximum tolerated dose (MTD) was reached as there were <33% of DLTs at each dose level explored.

Data with respect to cfDNA KIT mutational allele frequency, from in vitro studies as well as data from the dose-escalation phase, support the choice of RP2D.

Part 2 Dose-expansion Phase

The expansion phase of the study was initiated in 2017, using the RP2D, in order to further evaluate the safety, PK, PD, and evidence of anti-tumour activity across a variety of tumours with evidence of alterations in genes that are targets of ripretinib. Out of 10 planned cohorts, three included patients with GIST with KIT or PDGFRA mutation (also imatinib resistant mutations including KIT Exon 17 and PDGFRA D842V), that had progressed on or were intolerant to at least 1 line of systemic anticancer therapy.

All patients who received at least 1 dose of study drug were included in the safety analysis.

The interim CSR with a DCO on 01 Mar 2019, was based on the assessment of available data after completed enrolment of patients in 5 of the 10 planned cohorts. Once all cohorts are completely enroled additional analyses will be conducted on the entire study population and reported in a final CSR or separate report. Cohorts 1 through 3, in which GIST patients were included, are relevant for the present assessment.

KIT or PDGFRA Mutant Gastrointestinal Stromal Tumours

•Expansion Cohort 1 (4th line): up to 40 planned; 39 enroled

•Expansion Cohort 2 (>4th line): up to 35 planned; 36 enroled

•Expansion Cohort 3 (2nd and 3rd lines): up to 55 planned, at least 25 of these patients should have been second line patients; 55 enroled

Primary Objectives

• To further evaluate the safety and tolerability of oral ripretinib

• To determine the antitumour activity of ripretinib in all diseases under study

Secondary Objectives

• To determine the PK, including population PK, profile of oral ripretinib

• To evaluate the safety and tolerability of the RP2D of oral ripretinib in a cohort of patients with moderate and severe renal impairment

• To determine allele fraction of KIT and PDGFRA mutations in plasma cfDNA and compare it with mutation allele fraction in GIST tumour tissue and their association with prior treatment and study drug response

Exploratory Objectives

• To investigate the effects of ripretinib on selected pharmacodynamic parameters

• To determine allele fraction of KIT and PDGFRA mutations in plasma cell-free DNA (cfDNA) using NGS technique and compare it with mutation allele fraction in GIST tumour tissue and their association with prior treatment and study drug response

• To assess polymorphic variations in genes encoding drug metabolic enzymes and/or transporters involved in metabolism and disposition of ripretinib and DP-5439 and/or in genes that may potentially be associated with clinical response and/or study drug related toxicity

• To assess metabolic tumour response by 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) by European Organisation for Research and Treatment of Cancer (EORTC) criteria in selected patients

As of 01 Mar 2019, a total of 237 patients were enroled and received at least 1 dose of ripretinib during the dose escalation and expansion phases. At DCO there were 71 patients still on study treatment (12 (17%) patients in escalation phase; 59 (35%) patients in expansion phase). Of those, 181 patients in the escalation and expansion phases, who received ripretinib 150 mg QD, 117 (64.6%) patients discontinued from treatment and 64 (35.4%) patients were ongoing. Primary reasons for treatment discontinuation were progressive disease (66 patients; 36.5%) and adverse event (16 patients; 8.8%).

The cohorts included patients with GIST, receiving study drug ripretinib as 2nd- or 3rd-, 4th- or >4th line treatment and data on prior therapies for the treatment of GIST for those who received the ripretinib 150 mg QD dose show: 31 patients receiving ripretinib as 2nd line treatment, 28 patients receiving ripretinib as 3rd line treatment and 83 patients ripretinib as ≥4th line treatment. Furthermore, all patients, but 5 out of the 142 patients (96,5%), had received earlier treatment with TKIs. The type of last prior line of therapy was not presented, but none or very few of the patients had CR or PR as Best Overall Response to last prior therapy. A majority of the patients had discontinued their prior treatment due to progressive disease.

There were few patents discontinuing ripretinib treatment or study participation due to AEs. The most common reason for treatment discontinuations was progressive disease and the most common reason for study discontinuation was death. At DCO, 38.7% of the patients were still ongoing.

The evaluation of the antitumour activity of ripretinib included objective response rate (ORR) and disease control rate (DCR). Other endpoints included time to response (TTR), progression-free survival (PFS), and duration of response (DOR).

The median follow-up for ripretinib 150 mg QD dose (n=142) was 9.69 months, irrespective of line of therapy. The median relative dose intensity of ripretinib were comparable, irrespective of line of therapy.

Best Overall Response Rate Based on Investigator Assessment by Line of Therapy in Patients with GIST who Received 150mg QD in Escalation and Expansion Phases (ITT Population)

Parameters	2nd Line (N=31)	3rd Line (N=28)	4th Line (N=46)	>4th Line (N=37)	≥4th Line (N=83)	Total (N=142)
Best Overall Response n (%)						
Confirmed Partial Response	6 (19.4)	4 (14.3)	5 (10.9)	1 (2.7)	6 (7.2)	16 (11.3)
Stable Disease (≥6 weeks duration)	21 (67.7)	18 (64.3)	26 (56.5)	23 (62.2)	49 (59.0)	88 (62.0)
Progressive Disease	4 (12.9)	6 (21.4)	12 (26.1)	10 (27.0)	22 (26.5)	32 (22.5)
Not Evaluable	0	0	1 (2.2)	0	1 (1.2)	1 (0.7)
No Response Assessment	0	0	2 (4.3)	3 (8.1)	5 (6.0)	5 (3.5)
Objective Response Rate [a] n (%)	6 (19.4)	4 (14.3)	5 (10.9)	1 (2.7)	6 (7.2)	16 (11.3)
95% CI	7.5, 37.5	4.0, 32.7	3.6, 23.6	0.1, 14.2	2.7, 15.1	6.6, 17.7
Time to Response (Weeks) [b]	6	4	5	1	6	16
Mean (SD)	19.4 (9.53)	12.4 (8.43)	26.8 (21.42)	8.1 (--)[d]	23.7 (20.62)	19.2 (14.38)
Median	16.6	8.2	24.0	8.1	16.1	16.2
Min, Max	7.6, 35.9	8.0, 25.0	7.9, 59.1	8.1, 8.1	7.9, 59.1	7.6, 59.1
Best Overall Response n (%)						
Partial Response (confirmed + unconfirmed)	9 (29.0)	6 (21.4)	8 (17.4)	1 (2.7)	9 (10.8)	24 (16.9)
Stable Disease (≥6 weeks duration not required)	18 (58.1)	16 (57.1)	25 (54.3)	23 (62.2)	48 (57.8)	82 (57.7)
Progressive Disease	4 (12.9)	6 (21.4)	11 (23.9)	10 (27.0)	21 (25.3)	31 (21.8)
No Response Assessment	0	0	2 (4.3)	3 (8.1)	5 (6.0)	5 (3.5)
Complete/Partial Response Rate (confirmed + unconfirmed) n (%)	9 (29.0)	6 (21.4)	8 (17.4)	1 (2.7)	9 (10.8)	24 (16.9)
95% CI	14.2, 48.0	8.3, 41.0	7.8, 31.4	0.1, 14.2	5.1, 19.6	11.1, 24.1
Disease Control Rate [c]						
At 26 Weeks n (%)	18 (60.0)	15 (55.6)	20 (45.5)	9 (26.5)	29 (37.2)	62 (45.9)
95% CI	40.6, 77.3	35.3, 74.5	30.4, 61.2	12.9, 44.4	26.5, 48.9	37.3, 54.7
At 52 Weeks n (%)	8 (32.0)	8 (30.8)	10 (24.4)	3 (9.1)	13 (17.6)	29 (23.2)
95% CI	14.9, 53.5	14.3, 51.8	12.4, 40.3	1.9, 24.3	9.7, 28.2	16.1, 31.6

Abbreviations: CI = Confidence interval with Clopper-Pearson method; NE = Not Estimable

[a] Objective response rate is defined as proportion of patients who have a confirmed complete or partial response.

[b] Time to Response in weeks is defined as time from Cycle 1 Day 1 to first assessment of complete response or partial response which was subsequently confirmed.

[c] Disease Control Rate is calculated as the proportion of patients who have achieved response or stable disease and have no disease progression at 26 and 52 weeks, among patients who have not had their first disease progression or death yet by the corresponding time point.

[d] Only 1 patient had a confirmed partial response; SD could not be calculated.

Note: Line of therapy is 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 is counted as a single line of treatment. If the same drug is combined with a second drug, it is counted as a separate line of therapy. A patient having received, for example, 3 distinct treatment regimens (single agent or combination) would be considered a 4th line patient.

Source: Table 14.2.1.4

Duration of Response Based on Investigator Assessment by Line of Therapy in Patients with GIST who Received 150 mg in Escalation and Expansion Phases (ITT)

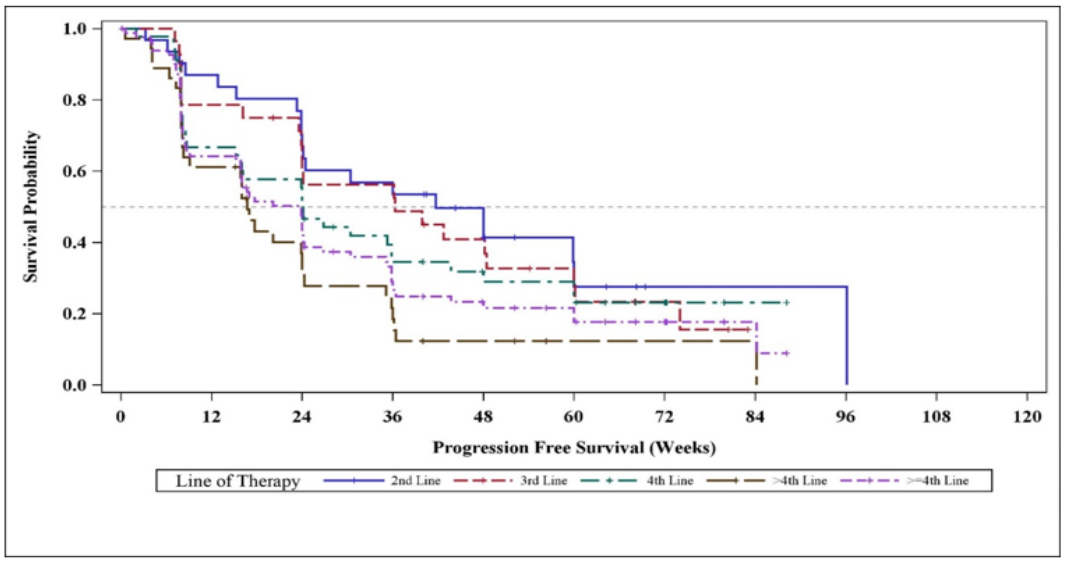
	2nd Line (N=31)	3rd Line (N=28)	4th Line (N=46)	>4th Line (N=37)	≥4th Line (N=83)	Total (N=142)
Number of Patients with Event n (%)	2 (6.5)	1 (3.6)	1 (2.2)	1 (2.7)	2 (2.4)	5 (3.5)
Number of Patients Censored n (%)	4 (12.9)	3 (10.7)	4 (8.7)	0 (0.0)	4 (4.8)	11 (7.7)
Kaplan-Meier Estimate of Duration of Response (weeks) 25th Percentile	80.0	NE	NE	76.1	76.1	76.1
95% CI	24.7, 80.0	52.1, NE	24.1, NE	NE, NE	24.1, NE	24.1, 80.0
50th Percentile	80.0	NE	NE	76.1	76.1	80.0
95% CI	24.7, 80.0	52.1, NE	24.1, NE	NE, NE	24.1, NE	52.1, NE
75th Percentile	80.0	NE	NE	76.1	NE	NE
95% CI	24.7, 80.0	52.1, NE	24.1, NE	NE, NE	24.1, NE	76.1, NE
Probability of Maintaining Response Status (%)						
12 Weeks %	100.0	100.0	100.0	100.0	100.0	100.0
95% CI	100.0, 100.0	100.0, 100.0	100.0, 100.0	100.0, 100.0	100.0, 100.0	100.0, 100.0
26 Weeks %	80.0	100.0	75.0	100.0	80.0	85.7
95% CI	20.4, 96.9	100.0, 100.0	12.8, 96.1	100.0, 100.0	20.4, 96.9	53.9, 96.2
52 Weeks %	80.0	100.0	75.0	100.0	80.0	85.7
95% CI	20.4, 96.9	100.0, 100.0	12.8, 96.1	100.0, 100.0	20.4, 96.9	53.9, 96.2

Abbreviations: CI = Confidence Interval; NE = Not Estimable

Note: Duration of response in weeks is defined as the time from first complete response or partial response which was subsequently confirmed until the time of disease progression or death by any cause. Line of therapy is 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 is counted as a single line of treatment. If the same drug is combined with a second drug, it is counted as a separate line of therapy. A patient having received, for example, 3 distinct treatment regimens (single agent or combination) would be considered a 4th line patient.

Source: Table 14.2.2.4

Kaplan-Meier Plot of PFS by Line of Therapy in Patients with GIST Receiving an Initially Assigned Dose of 150 mg QD in Escalation and Expansion Phases (ITT Population)



Abbreviations: DCC-2618=ripretinib; GIST=gastrointestinal stromal tumours; PFS=progression-free survival; QD=once daily; ITT=intention-to-treat
Note: PFS was defined as the time from Cycle 1 Day 1 to disease progression or death.
Source: DCC-2618-01-001 Interim CSR (01 Nov 2019) Figure 10.

Tumour regression was assessed by CT scans, however, up to Amendment 3, in addition, PET scans were performed. For the dose-escalation phase, partial metabolic response was seen across all dose-levels, however, a discrimination between doses was, however, not feasible. Furthermore, in patients progressing on the RP2D 150 mg ripretinib QD in the dose expansion phase and subsequently dose-escalated to 150 mg BID, partial metabolic response was seen in most of the 37 patients evaluable, regardless of line of therapy.

Tumour tissue KIT and PDGFR mutations available at study entry were a mix of mutation status at diagnosis, after last previous anticancer treatment and from the time of study entry, therefore do not necessarily represent mutation status at time of study entry for all patients. Mutation data were mainly presented for KIT and shows that KIT mutations were found in ~90% of the tissue samples and somewhat less in the cfDNA samples, without discriminating any differences with respect to line of treatment, and mainly found in exon 13 and 17. Analyses of association of specific mutations in tumour DNA with response to ripretinib and mutational status at the time of progression have not been performed.

Table 6: DCC-2618-01-001: Clinical Benefit (CR, PR, or SD with PFS of at least 16 weeks) by Line of Therapy and KIT Mutation in GIST Patients who Received Ripretinib 150 mg QD

LOT	KIT Exon	Clinical Benefit n (%)	Progressive Disease n (%)	Missing n	Total n
2nd and 3rd (N=7)	Exon 9 only	4 (100.0)	0	0	4
	Exon 9 + secondary mutations	1 (33.3)	2 (66.7)	0	3
≥4th (N=11)	Exon 9 only	2 (50.0)	2 (50.0)	1	5
	Exon 9 + secondary mutations	3 (50.0)	3 (50.0)	0	6
2nd and 3rd (N=27)	Exon 11 only	3 (60.0)	2 (40.0)	0	5
	Exon 11 + secondary mutations	18 (81.8)	4 (18.2)	0	22
≥4th (N=44)	Exon 11 only	5 (62.5)	3 (37.5)	0	8
	Exon 11 + secondary mutations	18 (51.4)	17 (47.2)	1	36

Abbreviations: CR=complete response; LOT=Line of Therapy; N=number of patients with ctDNA results, including patients with missing response; PFS=progression-free survival; PR=partial response; SD=stable disease.
Note: Calculation of percent responders excluded patients with missing response.
Data cut-off date: 31 Aug 2019

With respect to overall responses, there were no CRs. For all patients, escalation and expansion phases, (n=142), treated with ripretinib 150 mg QD, the ORR was 11.3%, compared to 14.3% for those who received ripretinib as the 3rd line therapy (n=28), 10.9% for those who received ripretinib as their 4th line therapy and 7.2% for those who received ripretinib as the ≥4th line therapy (N=83). For those patients who received ripretinib as 2nd line treatment (n=31) the ORR was 19.4%.

In comparison, it was noted that the same 142 patient cohort had an ORR (CR and PR) of 2.8% to their last prior treatment.

The disease control rate (response or stable disease), DCR, at 26 weeks were 45.9 % for all patients, 60% for 2nd line 55.6% for line 3rd line, 45.5% for 4th line and 37.2% for ≥4th line. At 52 weeks the DCR was 23.2% for all patients vs 17.6% for ≥4th line.

The probability of maintaining response status (all patients) at 52 weeks was 85.7% (95% CI 53.9, 96.2).

The KM estimate shows a median (50th percentile) of PFS at 23.9 weeks (95%CI = 15.9, 24.3) in GIST patients who received 150 mg QD as the ≥4th line of therapy (n=83, by INV) The probability of maintaining PFS for 52 weeks was 21.7% (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.

PFS by line of therapy showed a separation of the curves of each line of therapy.

The Kaplan-Meier estimate of median DOR was 76.1 weeks (95% CI 24.1, not estimable) among the 6 responders (PR; > 30% tumour size reduction) who received 150 mg QD as the ≥4th line of therapy in the Escalation and Expansion phases.

2.5.1.2. Main study

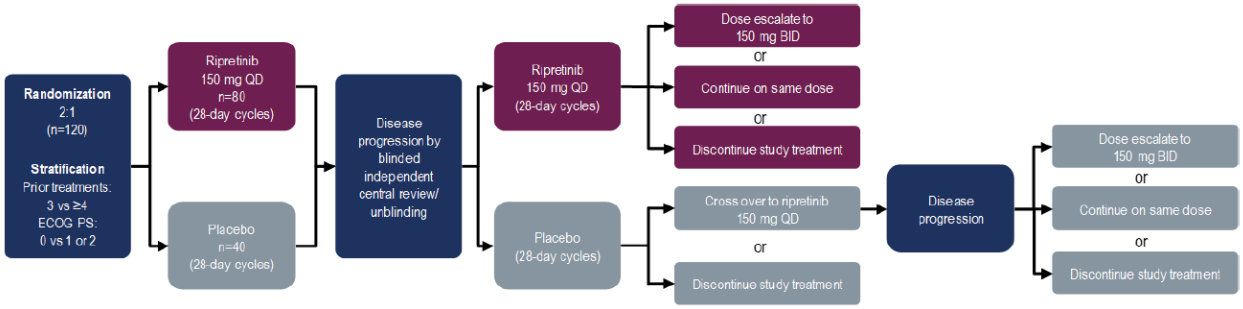
DCC-2618-03-001

Study DCC-2618-03-001 (INVICTUS) is an ongoing, Phase 3, 2-arm, randomised, placebo controlled, double-blind, international, multicentre study comparing the efficacy of ripretinib + BSC to placebo + BSC in patients who had received previous treatments with at least 3 prior TKI therapies (imatinib, sunitinib, and regorafenib). Data cut-off: 31 May 2019.

INVICTUS provides the primary data in support for the clinical efficacy of ripretinib. The target dos, 150 mg QD, was based on RP2D chosen based on data from the escalation phase in the dose-response study DCC-2618-01-001.

Tumour assessments were performed using the GIST specific mRECIST criteria Version 1.1 (modified with respect to non-nodal or non-bone target lesions, Demitri et al 2013b) and based on independent radiologic review (IRR).

Study Design



Abbreviations: BID = twice daily; ECOG PS = Eastern Cooperative Oncology Group Performance Status; QD = once daily
Randomization was stratified based on prior lines of therapy (3 vs > 3) and ECOG (0 vs 1 or 2) per protocol.

A total of 129 subjects were enroled for treatment in the double-blind period and all 129 were analysed in the ITT population. The study was performed in 12 countries; US [47%], Canada, Australia, Singapore. From the EU [44%] (France Germany, Italy, The Netherlands, Poland, Spain, UK and Belgium).

Study participants

The key inclusion criteria were adult patient, with a histological GIST diagnosis, required to have progressed on imatinib, sunitinib, and regorafenib or have documented intolerance to any of these treatments despite recommended dose modifications. Access to archival tumour tissue sample if no anticancer therapy had been administered since the sample collection; otherwise, a fresh tumour tissue sample. ECOG PS of 0 to 2 and adequate organ function and bone marrow reserve.

The key exclusion criteria were concurrent malignancy, CNS metastasis, NYHA II-IV, uncontrolled hypertension or heart failure, thrombo-embolic events within 6 months, LVEF <50% and gastrointestinal abnormalities (e.g., post-operative consequences), QTcF prolongation or history of long QT syndrome; LVEF <50%, or any medication that could interfere with the assessment of ripretinib.

Treatments

Patients were randomized in a 2:1 fashion to ripretinib 150 QD (as 50 mg strength tablets), orally, with or without food) or to placebo.

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. Dose reduction occurred in reductions of 50 mg.

The study had two main treatment periods, the double-blind treatment analysis period in which patients received their randomised assigned treatment and the open-label treatment analysis period for patients with progressive disease, either crossing over from the placebo arm or patients who

continued receiving ripretinib, either as initially assigned, 150 mg QD or after dose-escalation to 150 mg ripretinib BID.

Prohibited medications and other restrictions

The following medications were excluded during the study: Proton pump inhibitors, strong or moderate inhibitors or inducers of CYP3A4, including certain herbal medications (e.g., St. John's Wort), grapefruit or grapefruit juice; known substrates or inhibitors of breast cancer resistance protein (BCRP) transporters, anticancer therapies, including investigational therapy.

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

Objectives/ endpoints

The **primary objective** was to determine the efficacy (PFS) of ripretinib by independent radiologic review (IRR, by mRECIST v 1.1) in patients with advanced GIST who had received prior anticancer therapies.

The **secondary objectives** were to determine the ORR (key) by IRR, to assess TTP, OS, DoR, and DCR, to assess the PK/PD relationship of ripretinib and to assess the robustness of efficacy using a sensitivity analysis. Furthermore, to assess the safety of ripretinib and disease-related symptoms and quality of life.

Main exploratory endpoints were assessment of ripretinib efficacy on dose escalation to ripretinib 150 mg twice daily (BID). To characterize KIT and PDGFRA gene resistance mutations (and potentially other gene mutations) and their ripretinib-driven longitudinal mutation allele frequency (MAF) changes in plasma cell-free deoxyribonucleic acid (cfDNA). Furthermore, to retrospectively correlate KIT and PDGFRA mutation/s and/or their frequency (as well as of potentially other gene mutations) in baseline cfDNA with clinical benefit and to understand potential TKI-resistance mechanisms of GIST at time of progression.

Exploratory objectives as characterization of KIT and PDGFRA gene resistance mutations and their ripretinib-driven longitudinal MAF changes in plasma cfDN, is planned and results will be presented post-approval.

Randomisation and blinding

Subjects in this study were randomized, in a 2:1 ratio, into the 2 treatment arms and the randomization was stratified by 3 prior anticancer treatments versus ≥ 4 prior anticancer treatments and ECOG = 0 versus ECOG = 1 or 2. The randomisation procedure and the stratifications, appears appropriate.

2.5.1.2.1. Statistical methods

Based on the study design, there are two main analysis periods:

• Double-blind treatment analysis period included the period from the randomization date to the last follow-up date for patients who discontinued from the study upon disease progression (by IRR) on initial treatment or discontinuation from initial treatment due to other cause OR from the

randomization date to the first disease progression date, (this applies to patients who continued to receive ripretinib at 150mg QD or an escalated dose, 150 mg BID, or those who crossed over from placebo to receive ripretinib at 150mg QD after disease progression on initial treatment).

• Open-label analysis period included the period from the day immediately after the first disease progression (by IRR) on initial treatment to the last follow-up date for patients who continued to receive ripretinib 150mg QD or at an escalated dose and those who crossed over from placebo to receive ripretinib150mg QD after disease progression on initial treatment.

The primary efficacy endpoint, progression-free survival, was defined and analysed only during the double-blind treatment analysis period.

Overall survival is defined and analysed throughout patients' entire study period. The data cut-off for the primary analysis was planned to occur when 90 PFS events had occurred. It was expected that the primary analysis would occur approximately 6 months after last patient's enrolment.

Analysis populations

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

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

The Per Protocol (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.

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

Primary endpoint

The primary endpoint of PFS (reported in weeks) is defined as the 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. In the following situations, PFS will be re-defined otherwise or censored:

- For patients who do not have evaluable radio logic assessment (including those randomized but untreated due to death or any other cause), PFS will be censored at randomization date (PFS=1 day) unless they die within 2 cycles of treatment (8 weeks plus 3 days allowing for a late radio logic assessment within the visit window). If patients die within 2 cycles of treatment (8 weeks plus 3 days), they are considered to have a PFS event at death date
- For patients who only have non-measurable lesion according to modified RECIST Version 1.1 (non-nodal lesions must be ≥1.0 cm in the long axis or ≥double the slide thickness in the long axis) within 21 days prior to the first dose of study treatment, PFS will be censored at the date of latest evaluable progression-free radio logic assessment or patients will be considered to have disease progression at the date of new lesion(s) or unequivocal progression in non-target disease
- For patients who undergo surgical resection of target or non-target lesions, who have received other anticancer treatments than the study treatment before documented date of the first disease progression, PFS will be censored at the date of the latest evaluable progression-free radiologic assessment

- For patients who have not progressed and have not died, PFS will be censored at the time of the latest date of evaluable progression-free radio logic assessment if at most one missed/non-evaluable assessment prior to this assessment
- For patients who have first disease progression or die after two or more consecutive missed/non-evaluable assessments, the patient will be censored at the time of the evaluable radiologic assessment immediately prior to the two or more consecutive missed/non-evaluable radiologic assessments. The missed/non-evaluable assessments include both the scheduled assessments when a patient was on treatment and the hypothetical assessments (the expected assessments as if the patient was still on treatment) after a patient discontinued treatment or withdrew for reasons other than progressed disease. For patients who have first disease progression documented between scheduled assessments, progression date is defined as the date of new lesion (if progression is due to new lesions) or defined as the earliest of the scan dates of the components that triggered the progression per independent radio logic review (if progression is due to increase in sum of measured lesions).

Analysis for PFS will be stratified by the randomization stratification factors [prior lines of therapy (3 versus ≥4) and ECOG (0 versus 1 or 2)]. The p-value will be from a 2-sided stratified Log-rank test at 0.05 significant level for evaluation of treatment difference. Point estimate of hazard ratio will be obtained from a Cox regression model with treatment and the randomization stratification factors as fixed factors and it's 95% CI will be obtained using Wald method. PFS time will be summarized via KM methodology using the 25th, 50th (median), and 75th percentiles and pre-specified timepoints, each with associated 2-sided 95% confidence intervals. Analyses will be performed using the ITT population as the primary efficacy analysis and PP population as supportive.

Secondary endpoints

The key secondary endpoint, ORR, is defined as the proportion of patients with a confirmed complete response (CR) or partial response (PR) based on the independent radiologic review and during the initial assigned study treatment. This analysis will be performed in the ITT population as the main analysis and the PP population as supportive analysis. To be assigned a status of a CR or PR, changes in tumour measurements must be confirmed by repeat assessments that must be performed at least 4 weeks (allowing a minus 3-day window) after the criteria for response are first met. This analysis will include assessments prior to an event or censoring under the primary PFS analysis. Patients with unknown or missing response will be categorized as non-responders and will be included in the denominator when calculating the proportion. An unstratified two-sided Fisher's Exact test at a 0.05 significance level will be used to investigate statistical differences between treatment groups. A 95% Newcombe score confidence interval will be constructed for the treatment rate difference in ORR (Newcombe, 1998) A sensitivity analysis will be performed for ORR without requiring confirmation of CR and PR.

Time to Progression (TTP, reported in weeks) is defined as the interval between the date of randomization and the earliest documented evidence of first disease progression on initial treatment based on the independent radiologic review. Since dying without progression is a competing risk of progression, TTP is censored at death date for patients who died without disease progression. Additionally, in the following situations, TTP will be re-defined otherwise or censored:

- For patients who do not have evaluable radio logic assessment, TTP will be censored at randomization date (TTP=1 day) unless they die within 2 cycles of treatment (8 weeks plus 3 days allowing for a late radio logic assessment within the visit window). If patients die within 2 cycles of treatment (8 weeks plus 3 days), TTP will be censored at death date

- For patients who only have nonmeasurable lesion according to modified RECIST Version 1.1 (non-nodal lesions must be ≥1.0 cm in the long axis or ≥double the slide thickness in the long axis) within 21 days prior to the first dose of study treatment, TTP will be censored at the date of latest evaluable progression-free radiologic assessment or patients will be considered to have disease progression at the date of new lesion(s) or unequivocal progression in non-target disease
- For patients who undergo surgical resection of target or non-target lesions, who have received other anticancer treatments than the study treatment before documented date of the first disease progression, TTP will be censored at the date of the latest evaluable progression-free radiologic assessment
- For patients who have not progressed, TTP will be censored at the time of the latest date of evaluable progression-free radiologic assessment if at most one missed/non-evaluable assessment prior to this assessment
- For patients who have first disease progression after two or more consecutive missed/non-evaluable scheduled or hypothetical assessments, TTP will be censored at the time of the evaluable radio logic assessment immediately prior to the two or more consecutive missed/non-evaluable scheduled or hypothetical radiologic assessments
- For patients who have first disease progression documented between scheduled assessments, progression date is defined as the date of new lesion (if progression is due to new lesions) or defined as the earliest of the scan dates of the components that triggered the progression per independent radiologic review (if progression is due to increase in sum of measured lesions)

TTP will be analyzed in a similar fashion to PFS.

Overall survival (OS, reported in weeks) is defined as the interval between the date of randomization and date of death from any cause. Patients who are still alive or who are lost to follow-up will be censored at the date of last contact. OS will be analyzed during the entire study period in a similar fashion to PFS.

The time to response, based on the independent radio logic review, is 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 does not have confirmed CR. Patients who do not have a confirmed PR or CR will be censored at the date of the last assessment during the double-blind treatment analysis period. Time to response will be summarized and displayed using KM methods in a manner similar to the primary analysis of PFS.

The EORTC-QLQ-C30 will be summarized by scale. In all scales, a high scale score represents a higher response level. The scoring for this questionnaire will be done in 2 steps. First, calculate the average of the items that contribute to the scale. This will be used as the raw score for the scale, and secondly, apply a linear transformation to standardize the raw score, so that scores range from 0 to 100.

Changes from baseline to Day 1 of Cycle 2 in EORTC-QLQ-C30 Role function and Physical function will be compared between the two treatment arms using analysis of covariance (ANCOVA) model with the stratification factors as factors. If Day 1 of Cycle 2 value is missing, then the change from baseline to the end of initial study treatment will be used in the analysis.

EQ-5D-5L will be summarized overall by number and percentage for each level of each dimension. For pain/discomfort and usual activities, the Cochran–Mantel–Haenszel test will be used to test the change in response scale at Day 1 of Cycle 2 from baseline between DCC- 2618 and placebo. For EQ-5D-5L index (utility) score, an ANCOVA model with the stratification factors as factors will be used to compare the change at Day 1 of Cycle 2 from baseline between the two treatment arms. EQ-VAS will be

summarized using continuous descriptive statistics. Change in EQ-VAS score at Day 1 of Cycle 2 from baseline between the two treatment arms will be tested with a t-test.

Multiplicity

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

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

If any hypothesis test is not significant at alpha=0.05 level, the subsequently listed analyses will be viewed as descriptive.

Subgroup analysis

Subgroup analysis will be performed for the primary and key secondary efficacy endpoints defined by the following variables:

- 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 1/2)
- Number of prior therapies (3 vs ≥4)

Open label analysis period

The open-label analysis period will be further split into 2 sub-periods, prior to intra-patient dose escalation and post intra-patient dose escalation

Days on ripretinib treatment within the open-label analysis period for patients that crossed over to ripretinib will be defined from the first dose date after crossover.

Efficacy analysis during the open-label analysis period will be explored by analysis sub-periods. For patients who initially received placebo and subsequently crossed over to ripretinib treatment, PFS in the "Prior to intra-patient dose escalation" sub-period will be defined as the time interval from the date of the first dose of ripretinib to the earliest documented evidence of disease progression. PFS will be re-defined or censored as needed and analysed in a similar fashion to the primary efficacy endpoint.

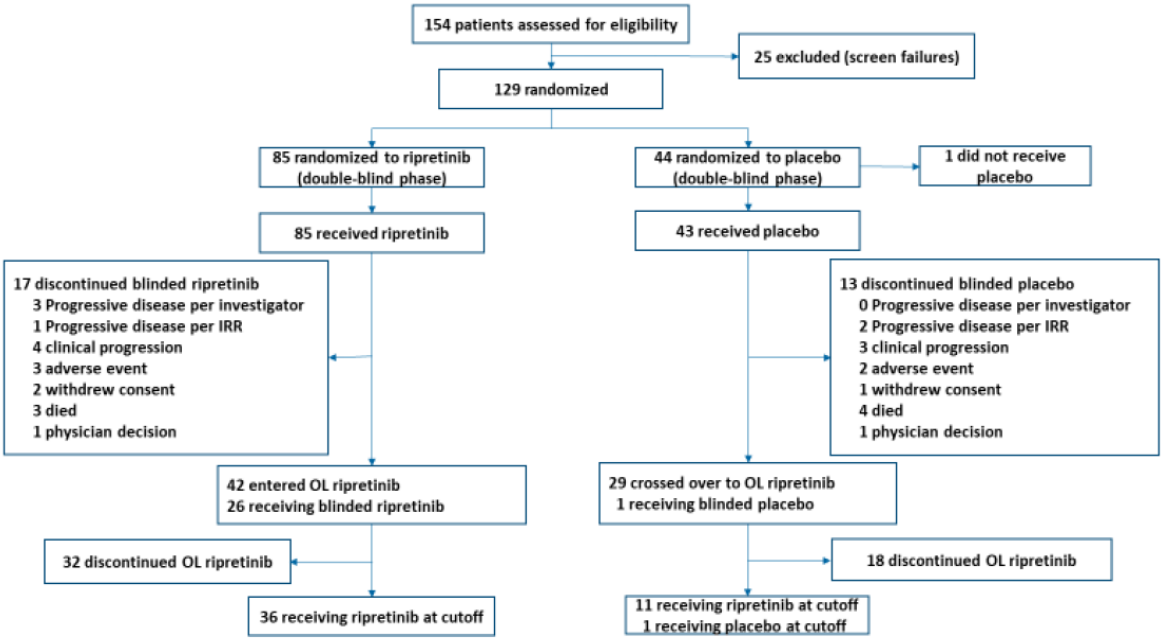
Amendments

There was a clinically important amendment (Amend. 3, 22 Mar 2018) when Patients with known KIT or PDGFRA *wild-type* GIST could be included.

2.5.1.2.2. Results

Participant flow

Patient Disposition by Double-blind and Open-label Periods



Double-blind Period

Patient Disposition (ITT population)

Category, n (%)	Placebo (N = 44)	Ripretinib (N = 85)	Total (N = 129)
Populations			
ITT Population	44 (100)	85 (100)	129 (100)
Safety Population	43 (97.7)	85 (100)	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[a]	29 (67.4)	42 (49.4)	71 (55.5)
Ongoing[a]	1 (2.3)	26 (30.6)	27 (21.1)
Discontinued Treatment[a]	13 (30.2)	17 (20.0)	30 (23.4)
Primary Reason for Treatment Discontinuation[a]			
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 IRR	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[b]	14 (31.8)	15 (17.6)	29 (22.5)
Primary Reason for Study Discontinuation[b]			
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
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 randomised. The safety population is defined as all patients who have received at least 1 dose of study drug. One patient was randomised 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 randomised 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 non-missing PK concentration in plasma reported for ripretinib or active metabolite, DP-5439
[a] Denominators are based on number of patients in the safety population
[b] Denominators for study discontinuation are based on number of patients in the ITT population
Source: DCC-2618-03-001 CSR (13 Nov 2019), Table 14

There were 129 patients enroled in the double-blind period in the ITT population. One patient was randomized to placebo but was never treated, and therefore not included in the safety population.

Overall, 30 of 129 patients (17 [20.0%] patients in the ripretinib arm and 13 [30.2%] patients in the placebo arm) discontinued treatment during the double-blind period. During the double-blind period, the most common reasons for treatment discontinuation were clinical progression (4.7% and 7.0% in the ripretinib and placebo arm respectively) and death (3.5% and 9.3% in the ripretinib and placebo arm, respectively) and AE (3,5% and 4,7% in the ripretinib and placebo arm respectively).

Out of 29 patients discontinuing the study during the double-blind phase, 25 was due to death, 14,1% and 29.5% in the ripretinib and placebo arm, respectively.

At DCO, 31 May 2019, 27 patients (21.1%), 26 patients vs one patient from the original ripretinib arm and placebo arm, respectively, were still receiving the blinded treatment.

Open-label Period

Patient Disposition (Safety Population)

Category, n (%)	OL: Ripretinib 150 mg QD (originally received placebo in double-blind period) (N = 29)	OL: Ripretinib 150 mg QD (originally received ripretinib in double-blind period) (N = 11)	Ripretinib 150 mg BID (N = 41)	Enter OL: Total (N = 71)
Ongoing	10 (34.5)	1 (9.1)	10 (24.4)	21 (29.6)
Discontinued Treatment	9 (31.0)	10 (90.9)	31 (75.6)	50 (70.4)
Primary Reason for Treatment Discontinuation				
Adverse Event	0	0	4 (9.8)	4 (5.6)
Clinical Progression	4 (13.8)	2 (18.2)	7 (17.1)	13 (18.3)
Death	0	1 (9.1)	2 (4.9)	3 (4.2)
Physician Decision	0	1 (9.1)	1 (2.4)	2 (2.8)
Confirmed Progressive Disease by Investigator Assessment	3 (10.3)	1 (9.1)	13 (31.7)	17 (23.9)
Confirmed Progressive Disease by IRR	0	2 (18.2)	2 (4.9)	4 (5.6)
Withdrawal of Consent from Study	1 (3.4)	1 (9.1)	1 (2.4)	3 (4.2)
Withdrawal of Consent from Treatment	1 (3.4)	1 (9.1)	0	2 (2.8)
Other	0	1 (9.1)	1 (2.4)	2 (2.8)
Discontinued Study	7 (24.1)	7 (63.6)	17 (41.5)	31 (43.7)
Primary Reason for Study Discontinuation				
Death	6 (20.7)	4 (36.4)	17 (41.5)	27 (38.0)
Withdrawal of Consent from Study	1 (3.4)	3 (27.3)	0	4 (5.6)

Abbreviations: BID = twice daily; OL = open-label; QD = once daily
Note: This summary includes patients that entered the open-label period and received ripretinib 150 mg QD and/or ripretinib 150 mg BID, with 2 analysis sub-periods (Prior to- or Post- Intra-Patient Dose Escalation to ripretinib 150 mg BID). Data from a single patient on open-label QD whose dose escalated to open-label BID can be presented in each Period
There were 2 patients who discontinued from treatment due to other reasons: 1 patient due to 'Off Study Drug for More Than A Cycle (28 Days)' and 1 patient due to 'Subject Started New Cancer Treatment'

There were 71 (55.5%) patients that had disease progression and entered the open-label period, including 42 (49.4%) patients from the ripretinib arm and 29 (67.4%) patients from the placebo arm.

Thirty-one patients receiving ripretinib 150 mg QD during the double-blind period, dose escalated to ripretinib 150 mg BID. Furthermore, 10 patients who crossed over to ripretinib upon progressive disease, subsequently dose escalated to receive 150 mg BID.

The main reason for treatment discontinuation during the open-label period, was progressive disease and the main reason for study discontinuation was due to death.

Baseline data

Demographics

The demographics and baseline characteristics were overall balanced. Overall, there was a slight male predominance, 75% were white and more than 90% had an ECOG score ≤1. The median age for all subjects was 60 years, however, there was a higher median age in the placebo group compared to the ripretinib group (64.5 years vs 59 years in the placebo group and ripretinib group respectively), specifically pronounced the group of 75 years or older (22.7% vs 9.4% in the ripretinib arm).

Inclusion allowed patients with ECOG PS 0-2, however, only 8.5% of the included patients belonged to the group of ECOG 2, with 63% having received 3 prior lines of therapy (37% ≥ 4 prior lines) and with a large proportion of elderly patients, 25% 65-74 years and 14% ≥75 years.

The median time since initial diagnosis was 5.69 years and very similar for both arms.

Tumour mutation

It is known that over 80% of GIST patients eventually develop disease progression driven by secondary-resistance mutations, located in additional KIT exons and PDGFRA, which constitutes the key reasons for resistance development in GIST. Genomic alteration of KIT/PDGFRA was planned to be retrospectively analyzed via central testing of tumour tissue after the inclusion. The CSR describes the mutational status for patients when included in the INVICTUS study. The most common genomic alteration (KIT/PDGFRA) was KIT exon 11 (58.1%), the second most common was KIT exon 9 mutations. Other than KIT exon 9 and 11 mutations were seen in only 3.1% and PDGFRA mutations 2.3%. However, these data do not necessarily reflect the full mutational complexity expected in ≥4th line GIST.

KIT and PDGFRA *wild type* GIST were reported for 7.8% of the included subjects (inclusion as of Amendment 3).

Prior systemic therapy

All patients had received at least 3 prior systemic anticancer therapies, i.e., the minimum stipulated by treatment inclusion criteria (imatinib, sunitinib and regorafenib), thirty-three (25.6%) patients had received 4 prior systemic therapies and 10 (7.8%) patients had 5 prior systemic therapies, i.e., the median number of prior treatments was 3. Eighty percent of the patients randomized to ripretinib had relapsed during the previous TKI treatment, while 23.5% were non-responders to the last previous therapy.

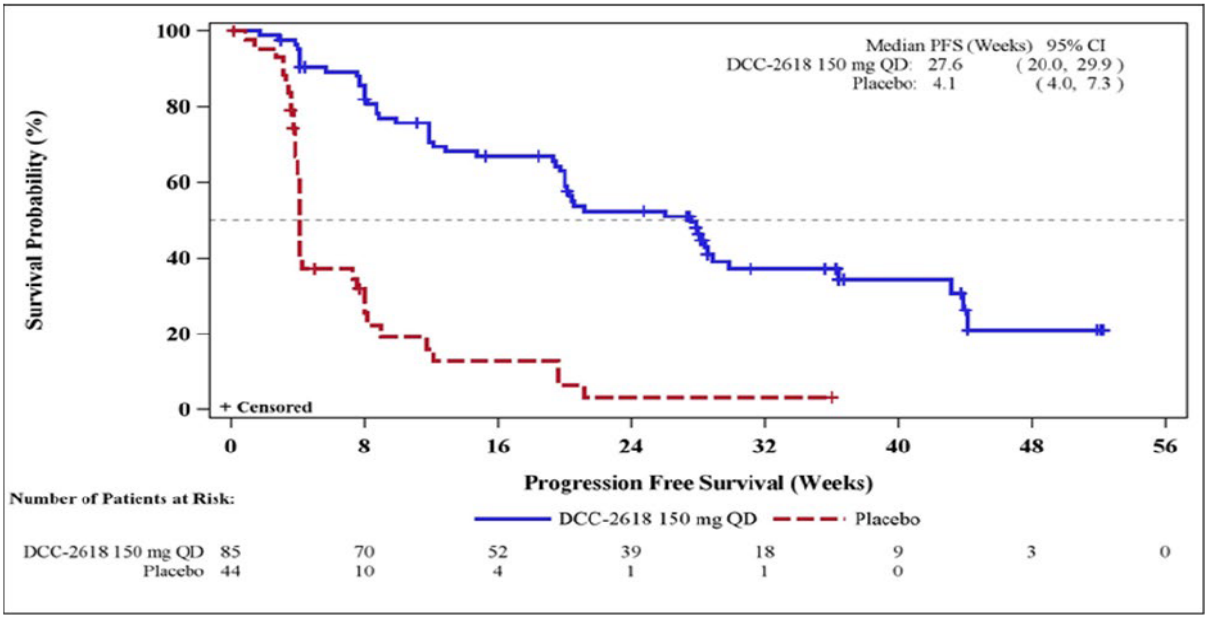
Outcomes and estimation

The analyses presented are based on the primary analysis with a data cut-off date of 31 May 2019. Treatment and follow-up are ongoing. 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, which is acceptable.

Please refer to the tabulated summary below for key outcomes.

- Primary endpoint: IRR-assessed PFS for ripretinib arm *vs* placebo, using a 2-sided stratified Log-rank test and stratified by the randomisation stratification factors (prior lines of therapy [3 vs. ≥4] and ECOG PS [0 vs.1 or 2]).

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: Figure 14.2.1.1; Listing 16.2.6.5.1

At DCO the event rate was 84.1% in the control arm vs 60% for the ripretinib arm, the primary outcome showed a HR of 0.15 (95% CI 0.09, 0.25): p<0,001 in favor of the ripretinib arm (the median FU for the double-blind period was not presented). Median PFS was 27.6 weeks (95% CI 20.0, 29.9) in the ripretinib arm compared to 4.1 weeks (95% CI 4.0, 7.3) in the placebo arm. Patients in the ripretinib arm had an 85% reduced risk of disease progression or death. This estimation is based on 18.8% progressive disease events and 14.1% deaths in the experimental arm, with the corresponding figures for the control arm being 63.6% and 29.5%, respectively.

Table 16: INVICTUS: Summary of Censoring Rules/Reason in Double-blind Treatment Period (ITT Population)

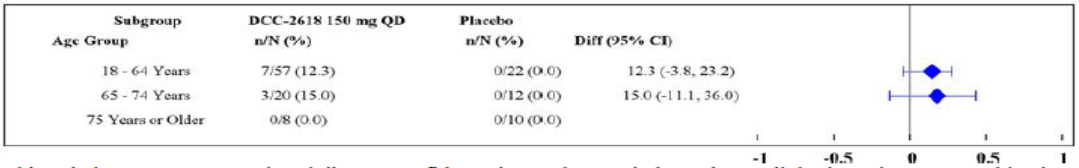
Categories, n (%)	Placebo (N=44)	Ripretinib (N=85)
Number of Events	37 (84.1)	51 (60.0)
Type of Event		
Disease progression	32 (72.7)	46 (54.1)
Death without disease progression	5 (11.4)	5 (5.9)
Number of Patients Censored	7 (15.9)	34 (40.0)
Type of Censoring		
No post-baseline evaluable assessment[a]	1 (2.3)	0
Received new anticancer therapy prior to progression/death[b]	2 (4.5)	6 (7.1)
In follow up for progression[c]	2 (4.5)	27 (31.8)
Unacceptable gap (≥2 missed/non-evaluable tumour assessments) between progression or death to the most recent prior evaluable assessment[d]	2 (4.5)	1 (1.2)

Abbreviation: ITT=intention to treat
[a] Patients without any post-baseline tumour assessments and who did not die within the first two cycles are censored at the randomisation date.
[b] Patients who received new anticancer therapy (including surgery and radiotherapy) before PFS event are censored at the date of the latest evaluable progression-free radiologic assessment prior to the new anticancer therapy.
[c] Patients who did not progress and did not die but had at least one evaluable post-baseline response assessments are censored at the last evaluable assessment.
[d] Patients with unacceptable gap (>=2 missed/non-evaluable tumour assessments) between progression or death to the most recent prior evaluable assessment are censored at the most recent evaluable assessment prior to the unacceptable gap.
Data cut-off date: 31 May 2019
Source: DCC-2618-03-001, Table Q92.1

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 used to assess the robustness of the result. 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.

In terms of HR for PFS, the subgroup analyses consistently favour the experimental arm, including the stratification groups (ECOG 0 vs 1 or 2) with a HR of 0.33 and 0.10, respectively, and number of prior treatments 3 vs ≥4 with a HR of 0.15 and 0.24, respectively. In addition, the median PFS for KIT/PDGFRA WT patients receiving ripretinib was 5.7 months, while the median PFS for KIT/PDGFRA WT patients receiving placebo was 2.1 months.

Figure 25: INVICTUS: Forest Plot of ORR Based on IRR by Patient Age (ITT Population)



Abbreviations: DCC-2618=ripretinib; CI=confidence interval; IRR=independent radiologic review; ORR=objective response rate; QD=once daily
Data cut-off date: 10 Aug 2020
Source: EMA D120 Figure 14.2.2.1.3

The results for ORR by age subgroup based on independent radiological review are summarized above. No responses were observed in patients 75 years or older. Among patients in the 18-64 years and 65-74 years subgroups, the ripretinib arm showed consistent benefit (difference is >0).

Sensitivity analysis of PSF by investigator assessment showed a discordance between IRR and INV assessed PFS on overall 20.2% in the double-blind period. The differences went in both directions,

however, the evaluation of progressive disease vs no progressive disease is obviously complex in GIST, with no bone lesions or no lymph nodes chosen as targets, instead the sources of assessments are estimations of solid or partly solid, heterogeneous masses (reflecting the presence of hemorrhage or cystic degeneration). The mRECIST allows for this assessment under these conditions.

Considering the complex circumstances of response assessment, the discordance, between IRR and INV, seems acceptable.

Additional sensitivity analyses were made for the PP population, i.e., PFS excluding subjects with important protocol deviations, HR 0.13 (95% CI [3] 0.08, 0.23) and the safety population, HR 0.15 (95% CI [3] 0.09, 0.25). The PFS result seems robust.

- Key secondary endpoint: ORR by IRR (alpha-controlled) unstratified two-sided Fisher's Exact test at a 0.05 significance level

ORR was based on IRR and during the initial assigned study treatment. The analysis was performed in the ITT population as the main analysis and the PP population as supportive analysis.

Summary of Objective Response Based on IRR in Double-blind Period (ITT Population)

Categories	Statistics	Placebo (N=44)	Ripretinib (N=85)	Ripretinib vs Placebo
Complete Response	n (%)	0	0	--
Partial Response	n (%)	0	8 (9.4)	--
Stable Disease (≥ 6 Weeks)	n (%)	9 (20.5)	56 (65.9)	--
Progressive Disease	n (%)	28 (63.6)	16 (18.8)	--
Not Evaluable	n (%)	3 (6.8)	4 (4.7)	--
No Response Assessment	n (%)	4 (9.1)	1 (1.2)	--
Objective Response Rate	n (%)	0	8 (9.4)	--
	95% CI [1]	0.0, 8.0	4.2, 17.7	
Fisher's Exact Test	p-value [2]	--	--	0.0504
Difference in Objective Response Rate	%	--	--	9.4
	95% CI [3]	--	--	0.2, 17.5

Abbreviations: CI = Confidence Interval; IRR= independent radiological review; ITT = intention-to-treat
[1] 95% CI is exact binomial confidence interval.
[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: Objective Response Rate is defined as the proportion of patients with a confirmed complete response or PR based on the independent radiologic review and during the initial assigned study treatment.
Note 2: Patients groups are based on the treatment initially assigned.
Source: Table 14.2.2.1.1.

The ORR in the ripretinib arm was 9.4 % vs 0% in the control arm, there were no CRs. Statistical significance at the 5% level was not achieved for the key secondary endpoint ORR (p=0.0504).

The rate of SD (≥6 weeks) was 65.9% in the ripretinib arm vs 20.5% in the control arm.

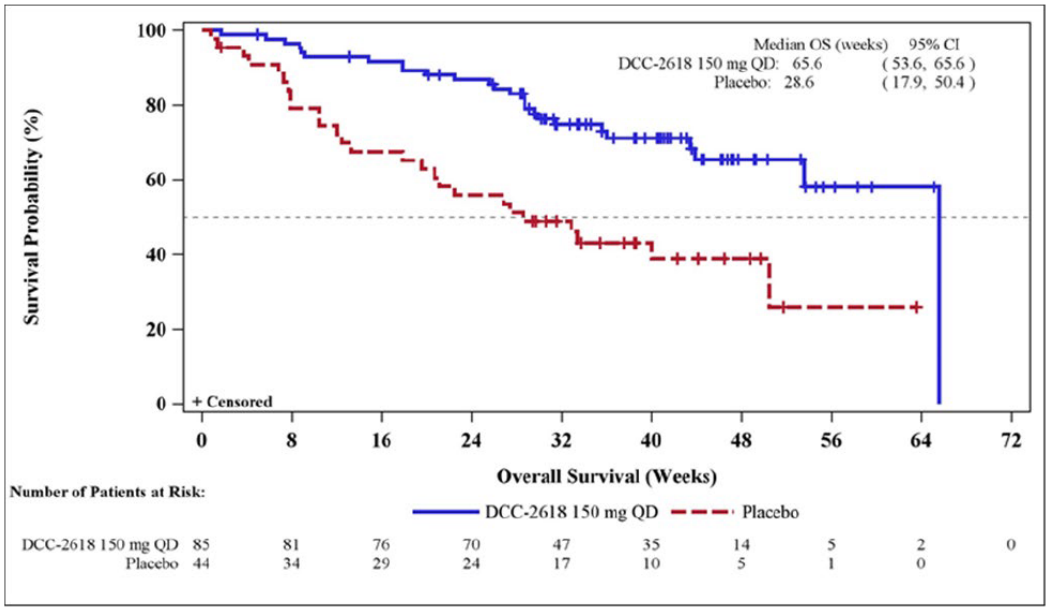
In terms of subgroup analysis of ORR, all groups were in favour of the ripretinib group. The most pronounced difference within a subgroup of is seen by gender and region.

The ORR in the PP population supports the overall results of ORR in the ITT population.

The ORR based on INV supported the overall ORR results by IRR. Statistical significance was not achieved for the key secondary endpoint ORR, and the hypothesis testing for the secondary endpoint OS, was therefore, not formally performed.

The OS data is presented according to the initial randomization assignment but defined and analysed throughout patients' entire on-study period.

Kaplan-Meier Plot of Overall Survival (ITT Population)



Abbreviations: CI = confidence interval; DCC-2618 = ripretinib; ITT = intention-to-treat; QD = once daily; OS = overall survival
Data cutoff: 31 May 2019
Source: Figure 14.2.4.

At data cut off the median OS was reached in both arms and the data is considered mature, 40% of the total death events had occurred. In the ripretinib arm 26 (30,6%) patients had died and 59 patients (69.4%) were censored, while in the placebo arm 26 (59.1%) had died and 18 (40.9%) were censored.

The median OS was 65.6 (CI 95% 53.6, 65.6) weeks for the ripretinib arm 28.6 (CI 95% 17.9, 50.4) weeks for the placebo arm. The OS data is confounded by censoring and the cross-over design. However, the risk of death was reduced by 64% in the arm with upfront ripretinib treatment, compared to the placebo arm, (HR = 0.36, 95% CI 0.21, 0.62); stratified log-rank test nominal p = 0.0004, (not statistically significant due to the prespecified hierarchical alfa-spending plan for the secondary endpoints).

At 26, 39 and 52 weeks the survival rate was 84,3%, 71,2 and 65,4% in the ripretinib arm and 55.9%, 43.1% and 25,9% in the placebo arm, respectively, a clear difference in support for the ripretinib treatment, which is illustrated by the KM curve.

- Median time to TTR is 8.1 weeks. The period from 4-8 weeks, counted from baseline, is also reflected in the PFS curve, for the ripretinib group this represents the period during which tumour growth decelerates and stabilizes in the ripretinib group while, for the placebo group, an early drop and a visible separation of the curve from the treatment group.
- Secondary endpoint: TTP, time to progression, evaluated during the initial assigned study treatment (interval between date of randomization and first documented evidence of progressive disease (IRR).

In the ripretinib arm 54.1% of the patients had TTP events vs 72.7% in the placebo arm. Median TTP was 28.0 (20.0, 36.4) weeks for the ripretinib arm and 4.1 (4.0, 7.6) weeks for the placebo arm.

- Secondary endpoint: DoR, Duration of response (double blind period)

Eight patients in the ripretinib arm showed a PR (ITT population). DoR for these eight patients were analysed; one patient progressed, one underwent salvage surgery and for the rest of the responding patients the median DoR was not reached at DCO.

- Disease-related symptoms and quality of life - Patient Reported Outcome Measurements

The PRO instruments were not used after verified progression. The stated objective was "to assess the improvement of disease-related symptoms". QOL as determined by changes from baseline to Day 1 of Cycle 2 in EORTC-QLQ-C30 Role function and Physical function was entered into the hierarchical testing strategy (each at 0.025 level significance). Thus, statistical significance was dependent on the success of the earlier tests in the hierarchy. If Day 1 of Cycle 2 value was missing, then the change from baseline to the end of initial study treatment will be used in the analysis". At cycle 2 day 1, approximately 80% of placebo patients had experienced progression, as opposed to around 20% in the active treatment arm. At Cycle 2 day 1, responses for 9/42 patients in the placebo group were missing, whereas the number of responses had increased from 74 at baseline to 79-80 in the active treatment arm.

Results with respect to the Open label treatment period

There were 71 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.

Time to crossover was defined as the time interval between the date of randomisation and the first date of ripretinib 150 mg dose for patients who initially received placebo and subsequently crossed over to ripretinib treatment. Of the 29 patients who originally received placebo in the double-blind period and crossed over to ripretinib 150 mg QD, the median (95% CI) estimated time to crossover was 6.6 (5.1, 9.1) weeks (data on file).

Out of the 29 patients crossing over to receive 150 mg ripretinib QD, 10 patients were ongoing at DCO. Ten (10) patients subsequently dose escalated to 150 mg ripretinib BID, only 1 patient was still ongoing at DCO.

Furthermore, there were 11 patients from the initial ripretinib 150 mg QD treatment arm who continued the same 150 mg QD dose in the open-label period, i.e., no dose-escalation. Only 1 patient was ongoing at DCO.

There were 31 patients, that received 150 mg QD in the double-blind period and after confirmed progressive disease, dose escalated to 150 mg ripretinib BID in the open label period, nine (9) of these patients were ongoing at DCO.

PFS (IRR) for Patients who Originally Received Placebo and crossed over to the Open-label Period (ITT Population)

Categories	Statistics	OL: Ripretinib 150 mg QD (originally received placebo) (N = 29)
Number of Patients with Event	n (%)	13 (44.8)
Number of Patients Censored	n (%)	16 (55.2)
Kaplan-Meier Estimate of Progression-Free Survival (Weeks)	25th Percentile (95% CI)	7.6 (2.4, 17.6)
	Median (95% CI)	20.0 (8.0, NE)
	75th Percentile (95% CI)	32.1 (20.0, NE)
Progression-Free Survival Rate		
26 Weeks	% (95% CI)	44.4 (21.7, 65.0)
39 Weeks	% (95% CI)	22.2 (1.8, 57.0)
52 Weeks	% (95% CI)	NE (NE, NE)

Abbreviations: CI = confidence interval; IRR= independent radiological review; ITT = intention-to-treat; NE = not estimable; OL = open label; QD = once daily
Note 1: Progression-free survival is defined as the time interval from the date of the first dose of ripretinib 150 mg once daily (QD) treatment in the open-label period to the earliest documented evidence of disease progression based on independent radiologic review or death, whichever comes earlier.
Note 2: This table only includes patients who originally took placebo and crossed over to ripretinib 150 mg QD treatment during the open-label period.
Source: Table 14.2.13.1.

Table 14.3.1.2
Treatment Exposure in Open Label Period
(Safety Population)

		Prior to Intra-Patient Dose Escalation			Post Intra-Patient Dose Escalation	Entire Open Label Period
Parameter	Statistics	DCC-2618 150mgQD (DB: Placebo) (N=29)	DCC-2618 150mgQD (DB: DCC-2618 150mg QD) (N=11)	All DCC-2618 150mg QD (N=40)	DCC-2618 150mg BID (N=41)	Total (N=71)
Treatment Duration (weeks) [1]	n	29	11	40	41	71
	Mean (SD)	16.87 (12.418)	5.23 (6.169)	13.67 (12.172)	14.79 (11.657)	16.24 (12.869)
	Median	12.00	3.86	8.64	15.14	15.14
	Min, Max	1.0, 44.1	0.3, 20.0	0.3, 44.1	0.1, 43.1	0.1, 57.1
Treatment Duration (months) [2]						
<1 Month	n (%)	3 (10.3)	6 (54.5)	9 (22.5)	10 (24.4)	16 (22.5)
1 - <3 Months	n (%)	12 (41.4)	4 (36.4)	16 (40.0)	10 (24.4)	17 (23.9)
3 - <6 Months	n (%)	7 (24.1)	1 (9.1)	8 (20.0)	15 (36.6)	24 (33.8)
6 - <12 Months	n (%)	7 (24.1)	0	7 (17.5)	6 (14.6)	13 (18.3)
≥ 12 Months	n (%)	0	0	0	0	1 (1.4)

[1] Treatment duration is calculated by analysis subperiod, Prior to- and Post- Intra-Patient Dose Escalation to DCC-2618 150mg BID. Treatment duration (weeks) = (date of last treatment - date of first treatment + 1)/7. For patients who have two subperiods, the end date of the Prior to Intra-Patient Dose Escalation subperiod is used as the date of last treatment for the first subperiod. Treatment duration in the entire Open-label period is calculated as the summation of the treatment durations in the two subperiods for patients who have both subperiods.
[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].
[3] Number of cycles = (date of last treatment – date of first treatment + 1)/28. Date of last treatment is defined as in footnote [1].
[4] Average Daily Dose = total dose received / treatment duration in days. Treatment duration in days is calculated as (date of last treatment - date of first treatment + 1) with date of last treatment defined as in footnote [1].
[5]Relative dose intensity = (total dose received /total planned dose)x100.
[6] Compliance = total number of days dosed / treatment duration in days x100. Treatment duration in days is calculated as (date of last treatment - date of first treatment + 1) with date of last treatment defined as in footnote [1]
Note: This summary includes patients that entered the Open Label Period and received DCC-2618 150mg QD and/or DCC-2618 150mg BID. Data from a single patient on open label QD whose dose escalated to open label BID can be presented in each subperiod. The number of patients in the 'Total' category represents all the patients who entered in the Open Label Period and may not be equal to the summation of the two subperiods. Table is supported by Listing 16.2.5.2

PROGRAM NAME: t_14_3_1_2_ex.sas Data cut-off date: 31MAY2019 DATE: 10:59/27SEP2019

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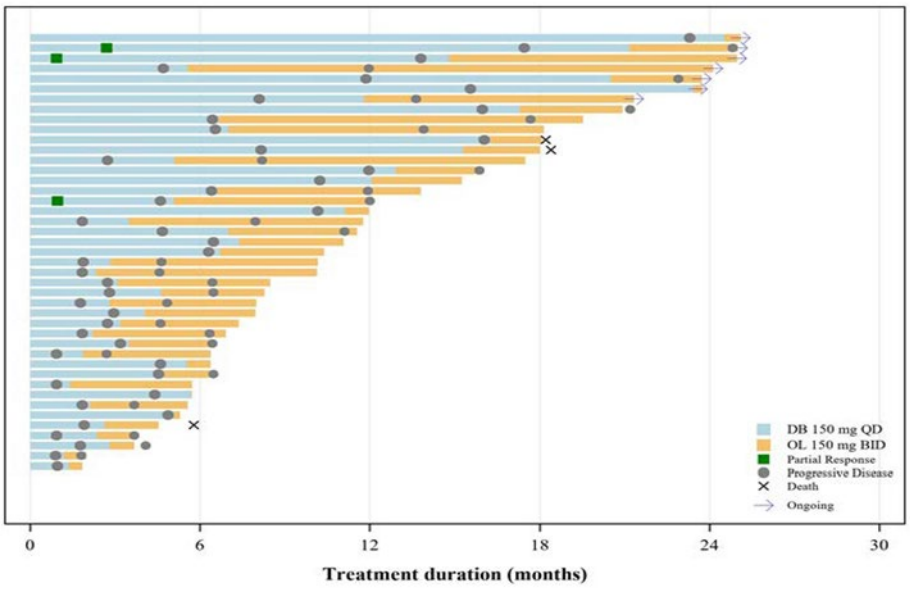
At DCO, close to 34% of the 71 patients entering the open label treatment period had been on treatment between 3 and 6 months and 18% had been on treatment between 6 and 12 months. The primary reason for treatment discontinuation was progressive disease.

Dose escalation

During the double-blind period of the INVICTUS study, patients in the ripretinib arm at the time of IRR progressive disease were offered the option to dose escalate to ripretinib 150 mg BID. Therefore, from the main study but also from the supportive study, data were generated on the doubling of the dose at the time of progression.

Figure 23: INVICTUS: Total Duration of Ripretinib Treatment in Patients Who Underwent IPDE during the Double-blind Period (ITT Population)



Abbreviations: BID-twice daily; DB=double-blind; OL=open-label; QD=once daily
Note: Of the 43 IPDE patients, 3 with progressive disease during ripretinib 150 mg QD were censored due to new anticancer therapy or surgery/radiation.
Data cut-off date: 10 Aug 2020
Source: DCC-2618-03-001, Figure Q96.10.2

The problem with these data is that there is no randomised control group to which outcomes can be compared and therefore, this does not isolate a drug effect. Furthermore, there are no objective responses to isolate drug effects (see discussion on clinical efficacy and B/R).

2.5.1.2.3. Summary of main efficacy results for trial DCC-2618-03-001

Title: Ripretinib is a kinase inhibitor indicated for the treatment of adult patients with advanced gastrointestinal stromal tumour (GIST) who have received prior treatment with three or more kinase inhibitors, including imatinib.		
Study identifier	DCC-2618-03-001 EudraCT Number 2017-002446-76	
Design	Phase 3, 2-arm, randomised (2:1), placebo controlled, double-blind, international, multicentre study of ripretinib 150 mg QD vs placebo	
	Duration of the double-blind treatment analysis period phase: Duration of the open-label analysis period:	Ongoing, patients may continue to receive ripretinib/placebo until precluded by toxicity, noncompliance, withdrawal of consent, physician decision, progressive disease, death, or closure of the study by the Sponsor. Ongoing. The open-label analysis period was split into 2 sub-periods, including the period prior to intra-patient dose escalation and the period post intra-patient dose escalation. Following progressive disease on ripretinib/or placebo patients could continue treatment, escalate to 150 mg BID or cross-over from placebo to active treatment.
Hypothesis	-The detection of a difference in PFS between DCC-2618 and placebo assuming a median PFS of 4.5 months for DCC-2618 and 1 month for placebo. - Objective response rate (ORR): 0.22 in the ripretinib arm vs. 0.02 month in the placebo arm	

Treatments groups	Active treatment: Patients with GIST who had received ⩾3 previous lines of therapy including 3 lines of TKI treatments		Oral dose of ripretinib 150 mg QD N=85
	Placebo: inclusion as above		Corresponding placebo tablets N=44
Endpoints and definitions:	Primary endpoint: Progression free survival	PFS (weeks)	Defined as the 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. Analysed only for the double-blind period.
	Secondary endpoint (key): Overall response rate	ORR (CR+PR) Based on mRECIST	Defined as the proportion of patients with a confirmed CR or PR based on the independent radiologic review and during the initial assigned study treatment
	Secondary endpoint: Overall survival	OS	The interval between the date of randomisation and date of death from any cause.
	Secondary endpoint: Time to progression	TTP	Date of randomisation and the earliest documented evidence of first disease progression on initial treatment (IRR)
Database lock	31 May 2019		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	ITT (all patients who signed the ICF and were randomized). The ITT population was used for all efficacy analysis as a primary analysis set with treatment assignment based on randomization.			
Descriptive statistics and estimate variability	Treatment group	Ripretinib 150 mg QD	Placebo	*Effect estimate per comparison*
	No of subjects	85	44	
	PFS Median (95% CI)	27.6 (20.0,29.9)	4.1 (4.0, 7.3)	HR; 0.15 (0.09,0,25) stratified log-rank; p < ,0001
	ORR, n (%) Difference in ORR (%, 95% CI)	8 (9.4) 9,4 (0.2,17.5)	0	nominal p-value: 0,0504
	CR n (%)	0	0	NE
	PR n (%)	8 (9.4)	0	see ORR
	OS (weeks) Median (95% CI)	65.6 (53.6, 65.6)	28.6 (17.9, 50.4)	HR 0,36 95% CI (0.21, 0.62) p-value; 0.0004 *

	TTP (weeks) Median (95% CI)	28.0 (20.0, 36.4)	4.1 (4.0, 7.6)	
Notes	For the primary endpoint PFS, all randomized patients were included in the primary analysis, with 34 patients in the ripretinib arm and 7 in the Placebo arm censored according to the rules pre-specified in the statistical analysis plan and as follows, o 27 patients in the ripretinib arm and 2 patients in the Placebo arm were censored at the last evaluable non-progressive disease assessment. o 1 placebo patient was censored at randomization date because of not being treated and no post-baseline assessment. o 6 patients in the ripretinib arm and 2 patients in the Placebo arm were censored at the last evaluable non-progressive disease assessment before starting new anti-cancer treatment or anti-cancer procedure. o 1 patient in the ripretinib arm and 2 patients in the Placebo arm were censored at the last evaluable non-progressive disease assessment because they did not have disease progression and died after 2 or more hypothetical assessments. When PFS was censored for a patient, the tumour assessments until the censoring date were used for the derivation of the best overall response. Exploratory Objectives, among others characterization of KIT and PDGFRA gene resistance mutations and their ripretinib-driven longitudinal mutation allele frequency changes in plasma cell-free deoxyribonucleic acid (cfDNA), retrospective correlates of KIT and PDGFRA mutation in baseline cfDNA with clinical benefit, potential TKI-resistance mechanisms of GIST at time of progression and efficacy of ripretinib in patients after dose escalation to ripretinib 150 mg twice daily (BID), will not be assessed within the present CSR. *not statistically significant due to the prespecified hierarchical alfa-spending plan			

Updated efficacy analyses

The most recent data cut-off, 10 Aug 2020 (another 14 months of FU) shows that of the 129 patients originally enroled, 6 patients randomised to ripretinib are still receiving ripretinib and 16 patients are receiving ripretinib as part of the open-label period.

Table 19: INVICTUS: Progression-free Survival Based on IRR in Double-blind Period (as of 10 Aug 2020)

Categories	ITT Population			PP Population		
	Placebo (N=44)	Ripretinib (N=85)	Ripretinib vs Placebo	Placebo (N=39)	Ripretinib (N=79)	Ripretinib vs Placebo
Number of Patients with Event, n (%)	37 (84.1)	68 (80.0)	-	34 (87.2)	64 (81.0)	-
Type of Event, n (%)						
Disease progression	32 (72.7)	62 (72.9)	-	30 (76.9)	59 (74.7)	-
Death without disease progression	5 (11.4)	6 (7.1)	-	4 (10.3)	5 (6.3)	-
Number of Patients Censored, n (%)	7 (15.9)	17 (20.0)	-	5 (12.8)	15 (19.0)	-
Type of Censoring, n (%)						
No post-baseline evaluable assessment[a]	1 (2.3)	0	-	5 (12.8)	15 (19.0)	-
Received new anticancer therapy prior to progression/death[b]	2 (4.5)	7 (8.2)	-	2 (5.1)	6 (7.6)	-
In follow up for progression[c]	2 (4.5)	9 (10.6)	-	1 (2.6)	8 (10.1)	-
Unacceptable gap (≥2 missed/non-evaluable tumour assessments) between progression or death to the most recent prior evaluable assessment[d]	2 (4.5)	1 (1.2)	-	2 (5.1)	1 (1.3)	-
Kaplan-Meier Estimate of Progression-Free Survival						
25th Percentile, Weeks (95% CI)	3.7 (3.1, 4.0)	11.9 (8.0, 19.3)	-	3.7 (3.1, 4.0)	9.9 (7.7, 14.7)	-
Median, Weeks (95% CI)	4.1 (4.0, 7.3)	27.6 (20.0, 35.3)	-	4.1 (3.9, 4.1)	26.0 (19.7, 28.9)	-
75th Percentile, Weeks (95% CI)	8.1 (4.1, 19.6)	51.7 (36.4, 67.9)	-	7.6 (4.1, 11.7)	44.4 (35.4, 60.1)	-
Cox Proportional Regression Model[e]						
Hazard Ratio	-	-	0.16	-	-	0.13
95% CI[f]	-	-	0.10, 0.27	-	-	0.07, 0.22
Progression-free Survival Rate						
26 Weeks, % (95% CI)	3.2 (0.2, 13.8)	51.0 (39.4, 61.4)	-	0.0 (NE, NE)	49.0 (37.1, 59.8)	-
39 Weeks, % (95% CI)	3.2 (0.2, 13.8)	35.5 (24.8, 46.2)	-	0.0 (NE, NE)	33.7 (22.9, 44.8)	-
52 Weeks, % (95% CI)	NE (NE, NE)	22.2 (13.4, 32.4)	-	0.0 (NE, NE)	20.9 (12.1, 31.3)	-
78 Weeks, % (95% CI)	NE (NE, NE)	11.8 (5.6, 20.6)	-	0.0 (NE, NE)	11.2 (5.0, 20.3)	-
104 Weeks, % (95% CI)	NE (NE, NE)	6.9 (1.9, 16.5)	-	0.0 (NE, NE)	6.4 (1.7, 15.9)	-

Abbreviations: CI=confidence interval; IRR=independent radiological review; ITT=intention-to-treat; NE=not estimable; PP=per protocol.
[a] Patients without any post-baseline tumour assessments and who did not die within the first two cycles are censored at the randomisation date.

Overall, PFS results from the 10 Aug 2020 data cut-off were similar in the ITT and PP populations. Compared to the previous data cut-off, the median Kaplan-Meier estimate was the same, and additional data were reported for 78 and 104 weeks. ORR was adjusted from 9.4% to 11.8% and median OS from 65,6weeks to 79.1 weeks (descriptive). These data are presented in the SmPC.

Analysis performed across trials

The randomised study, INVICTUS (DCC 2618-03-001), included GIST patients having already received at least the three lines of TKIs approved in this indication, studied ripretinib+ BSC vs BSC, with the primary endpoint of PFS. The dose-response study, DCC-2618-01-001, included a variety of tumours with evidence of alterations in genes that are targets of ripretinib, with the primary ambition to define the RP2D and using this dose to evaluate the safety and tolerability of oral ripretinib and determine the anti-tumour activity of ripretinib in all diseases studied. However, among other subgroups, a subgroup with GIST patients, receiving ripretinib in ≥4 line, was identified.

A comparison of baseline characteristics showed that there were no major differences with respect to gender, age, race, ethnicity or ECOG at screening. For tumour assessment, study DCC-2618 01-001 used RECIST by INV, while study INVICTUS (DCC 2618-03-001) as primary endpoint assessed tumour response according to mRECIST (v 1.1) by IRR. Furthermore, the exposure in Study DCC-2618-01-001 includes also exposure to ripretinib 150 mg BID for patients who experienced progressive disease, while the data presented for INVICTUS includes patients from the double-blind period separated from the open-label period. Therefore, the exposure between the two studies is not comparable.

Tables provided for this side-by side-comparison are misleading with regards to the prior lines of treatment received in the different study cohorts/treatment arms, and do not properly reflect relevant existing differences between studies.

A comparison between these two studies is, of many reasons, not statistically feasible, but the results from the dose-escalation study are not, however, challenging the results from the main study.

Clinical studies in special populations

-**GIST is very rare in children and adolescents.**

A full waiver has been granted on the basis of lack of significant benefit in the paediatric population by the PDCO.

-Patients with renal or hepatic impairment

No clinically meaningful effects on the PK of ripretinib were identified for mild to moderate renal impairment (baseline creatinine clearance 30 to <90 mL/min), or mild hepatic impairment (National Cancer Institute hepatic impairment categories B1 and B2). Since there were only 2 patients with moderate hepatic impairment and 4 patients with severe renal impairment, the data were insufficient for an assessment of the impact of moderate and severe hepatic impairment and severe renal impairment on ripretinib PK. No information is presented concerning efficacy and/or safety in these special populations. The applicant should provide any available information from ongoing studies and justify current SmPC recommendations.

-Elderly patients

No clinically meaningful effects on the PK of ripretinib were identified for age (19 to 87 years). Based on subgroup analyses provided, efficacy can be concluded across all age groups.

The table below has been completed by the applicant with the most updated information from ripretinib studies. In clinical studies, no clinically relevant differences were observed between elderly (aged >65 years and above) and younger patients (aged <65 and >18 years) which is included in the SmPC.

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Study: DCC-2618-03-001	32/129 (24.8)	18/129 (14.0)	38/277 (13.7)
Non-controlled Study: DCC-2618-01-001	65/277 (23.5)	38/277 (13.7)	6/277 (2.2)

Supportive study

Please refer to dose-response study presented above.

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The applicant has applied for a full marketing approval for the pan-KIT and PDGFRA inhibitor ripretinib for the indication

Qinlock is indicated for the treatment of adult patients with advanced gastrointestinal stromal tumour (GIST) who have received prior treatment with three or more kinase inhibitors, including imatinib.

- The pivotal study, DCC 2618-03-001 (INVICTUS) is an ongoing Phase 3, 2-arm, randomised (2:1), placebo-controlled, double-blind, multicentre study comparing the efficacy of ripretinib + best supportive care ("ripretinib arm") with placebo + best supportive care ("placebo arm"), in 129 adult patients with advanced GIST (85 vs 44 in the ripretinib and placebo arm, respectively), who had progressive disease on imatinib, sunitinib, and regorafenib or were intolerant to any of these treatments. Since there were no other EU approved treatment options at study initiation, the choice of BSC as the control arm, is justified. Patients received ripretinib 150 mg or placebo orally once daily until disease progression or unacceptable toxicity. Crossover was permitted at disease progression for patients randomised to receive placebo. Patients were stratified by prior lines of therapy (3 vs. ≥4) and EGOG PS (0 vs.1 or 2). Furthermore, intra-patient dose-escalation was possible after confirmed progression.

The primary efficacy outcome measure was progression-free survival (PFS) based on assessment by blinded independent central radiological review (IRR) using modified RECIST v1.1, in which lymph nodes and bone lesions were not target lesions and a progressively growing new tumour nodule within a pre-existing tumour mass must meet specific criteria to be considered unequivocal evidence of progression. Key secondary endpoint was ORR, while OS was another secondary endpoint.

The statistical methods are overall acceptable and match the study design. The analysis plan divides the study in the double-blind and open label period, which is an unusual way to describe an event driven study were unblinding takes place at the time of the PFS event, which is the primary endpoint. However, OS is analyzed regardless of period which would be expected.

The censoring rules for PFS is noted to be according to FDA guideline. The amount of and reason for censoring differ slightly between the treatment groups. Treating the censoring as uninformative, as in the primary statistical analysis, may introduce bias and lead to incorrect conclusions about the extent of the treatment difference. However, the results from the primary analysis are considered robust and the value of further sensitivity analyses are considered of limited value.

The procedure to control the type 1-error for multiple testing is a hierarchical testing procedure, testing the primary endpoint (PFS), key secondary endpoint (ORR), OS and quality of life sequentially. Testing is stopped when a test does not meet statistical significance at the 5%-level. The remaining analyses will be interpreted as descriptive and non-confirmative.

The analysis plan, mainly changing the analysis population for primary endpoint and to include stratification variables in the statistical test method, was changed in amendment 5 during the study. These changes do not cause concern since the changes made are for analyses that are preferred by the CHMP and would have been requested from the applicant if not included in the MAA.

The presented results were initially based on the primary analysis from May 2019 and an update on efficacy and safety data with the most recent cut-off date was provided by the applicant.

- Study DCC-2618-01-001, an open-label, multi-centre Phase 1 study to assess safety, tolerability, efficacy, and PK of ripretinib in adult patients with unresectable, metastatic GIST (also including other advanced malignancies with evidence of alterations in genes that are targets of ripretinib) who had received at least 1 prior anticancer therapy. The study design consists of two parts: a dose escalation part (Part 1, completed), and a dose expansion part (Part 2, ongoing). During Part 1, escalating doses were evaluated for safety and tolerability and determination of RP2D. Determination of PK profile as well as documentation of preliminary evidence of ripretinib antitumour activity in patients with advanced malignancies was also planned. During Part 2, additional patients were to, be included into 10 different cohorts (n=237), of which 3 included GIST patients, all receiving the selected PR2D of ripretinib.

In all 142 GIST patients were treated with ripretinib 150 mg QD during the phase 1 study.

Tumour assessment was performed using RECIST criteria (v1.1) and emphasis was borne down on results for all 142 GIST patients at the RP2D and including those 83 GIST patients who received the RP2D as the ≥4th line of treatment. The primary objective was to further evaluate the safety and tolerability of ripretinib and to determine the antitumour activity. Other objectives were to determine the PK profile, safety and tolerability of RP2D in patients with moderate and severe renal impairment.

Efficacy data and additional analyses

Efficacy results for the Pivotal study, DCC 2618-03-001 (INVICTUS)

Patient characteristics of the intent-to-treat (ITT) population in INVICTUS were median age of 60 years (range: 29 to 83 years), with 39% aged ≥65 years; 57% were male; 75% were white; and 92% had an ECOG performance status of 0 or 1. Sixty-three percent (63%) of patients received 3 prior therapies and 37% received 4 or more prior therapies. Sixty-six percent (66%) of patients randomized to placebo switched to ripretinib after disease progression.

Inclusion allowed patients with ECOG PS ≥ 2, however, only 8.5% of the included patient had ECOG PS 2, 63 % had received 3 prior lines of therapy (37% ≥4 prior lines) and a large proportion of elderly (24.8% of the patients in the age range of 65 to 74 years and 18 (14.0%) patients were ≥ 75 years of age.

The study showed a high treatment compliance.

The trial demonstrated a statistically significant improvement in PFS for patients in the ripretinib arm compared with those in the placebo arm (hazard ratio [HR] 0.15; 95% confidence interval [CI] 0.09, 0.25; p < 0.0001). The median PFS was 27,6 weeks (95% CI 20.0, 29,9) for ripretinib compared with 4.1 weeks (95% CI 4.0, 7.3) for placebo.

The ORR was 9% (95% CI 4.2, 18) in the ripretinib arm compared with 0% (95% CI 0, 8) in the placebo arm (nominal p-value = 0.0504 by Fisher's exact test). Consequently, ORR failed to show a statistical significance on the 5% level.

The median OS in the ripretinib arm was 65.6 weeks (i.e., 15.1 months) (95% CI 53.6, 65.6) compared with 28.6 weeks (95% CI 17.9, 50.4) in the placebo arm 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 pre-specified hierarchical multiple testing plan for secondary endpoints (i.e., PFS, then ORR, then OS). The clinical relevance of the OS results is, however, undisputable.

The PFS data was further supported by other secondary endpoints like TTP.

Furthermore, the clinical significance of ripretinib treatment was also demonstrated by patients after confirmed progressive disease, crossed over from the placebo arm to the open label treatment of ripretinib, who gained a further 20.0 (8.0, NE) weeks with stable disease.

Updated efficacy data with DCO 10 Aug 2020, demonstrated continued efficacy with ripretinib for patients with advanced GIST with regard to key efficacy results for the double-blind period (ITT and PP populations) and crossover patients in the open-label period.

Supportive evidence of efficacy

Phase 1, Study DCC-2618-01-001

Results from Part 1, dose escalation:

1) 3 DLTs were reported

2) MTD was not reached

3) RP2D selected was 150 mg QD.

Efficacy results from Part 2, (interim data, as of 01 Mar 2019), included patients with advanced GIST who had received ripretinib 150 mg QD as either 2nd line (N=31), 3rd line (N=28) or ≥4th line (N=83), in all 142 patients.

ORR displayed no CRs but PR rates reported for all patients were 11.3%, and for those who received ripretinib as their 4th line therapy 10.9% and for those who received ripretinib as the ≥4th line therapy 7.2%.

Kaplan-Meier estimate of median (50th percentile) PFS (by INV) was 23.9 weeks (95% CI 15.9, 24.3) for patients who received treatment as the ≥4th line of therapy

The Kaplan-Meier estimate of median duration of response was 76.1 weeks in 6 responders who received 150 mg QD as the ≥4th line of therapy in the Escalation and Expansion Phases,

Results in the cohort of patients who received ripretinib as a ≥ 4th line therapy appear consistent to those seen in the phase 3 trial, which is considered relevant supportive evidence.

Long-term studies with ripretinib have not been conducted. Both Study DCC-2618-01-001 and Study DCC-2618-03-001 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.

Claim for dose escalation after progression

The problem with the dose escalation data is that there is no randomised control group to which outcomes can be compared and therefore, this does not isolate a drug effect. Furthermore, there are no objective responses to isolate drug effects.

Consequently, the demonstration of clinical utility depends on an intra-patient comparison of PFS2 and PFS1, where time from PFS1 to PFS2 is shorter than is PFS1. Therefore, the intra-patient comparison of PFS is subject to uncertainty. In conclusion, it may be that the dose increase option after progression provides clinical benefit. However, data are not robust enough to support a claim for this treatment strategy in the SmPC

2.5.3. Conclusions on clinical efficacy

The clinical relevance of efficacy shown, in patients with advanced GIST having received three prior lines of TKI treatments, is unambiguous. Notwithstanding the failure to show ORR significance on the 5% level, the results of OS and other secondary endpoints like TTP are reassuring. In addition, patients crossing over from placebo to open label ripretinib, also gained a substantial PFS benefit.

The Phase 1 study (Study DCC-2618-01-001) provide data in support for a meaningful benefit by ripretinib to GIST patients.

2.5.4. Clinical safety

The applicant has provided in the initial submission, an integrated safety analysis using data from the pivotal study DCC-2618-03-001 (INVICTUS) and study DCC-2618-01-001 at the data cut-off dates of 31 May 2019 (date that the study was unblinded), and 01 Mar 2019, respectively. An additional 90-day

safety update at the request of FDA following the NDA submission with cut-off of 31 Aug 2019, has also been provided.

The integrated safety analysis includes three main components:

- **Pool 1** - DCC-2618-03-001 (INVICTUS): Includes the subsets of patients receiving 150 mg QD, patients who were dose escalated to 150 mg BID and patients who originally received placebo and subsequently crossed over to ripretinib; N=114
- **Pool 2** - The 150 mg QD subset and the safety data collected from both studies, also including patients who were dose escalated to 150 mg BID; N=256
- **Pool 3** - All patients from both studies in the safety population and the safety data collected on/after ripretinib treatment; N=372

2.5.4.1. Patient exposure

Summary of Exposure to Ripretinib in Clinical Studies Included in the SCS

Study	Any Exposure to Ripretinib	Exposure to Ripretinib 150 mg QD	GIST patients Exposed to Ripretinib 150 mg QD
Patient Studies			
DCC-2618-03-001	114	114	114
DCC-2618-01-001	237	181	142
Total patients	351	295	256
Healthy Subject Studies			
DCC-2618-01-002	50	10	0
DCC-2618-01-003	45	0	0
Total healthy subjects	95	10	0
Total Exposure	**446**	**305**	**256**

Abbreviations: GIST=gastrointestinal stromal tumour; MAA=Marketing Authorization Application; QD=once daily.
Sources: Study DCC-2618-03-001 CSR, Tables 14.3.1.1 and 14.3.1.2 (data cutoff: 31 May 2019); Study DCC-2618-01-001 Interim CSR, Table 14.3.1.2 (data cutoff: 01 Mar 2019); Study DCC-2618-01-002 CSR Table 14.1.2.1 and 14.1.2.2; Study DCC-2618-01-003 CSR, Tables 14.1.1.1 and 14.1.1.2.

Safety data from a total of 446 patients with any exposure to ripretinib is included in the submission. Of these, 351 patients had advanced malignancies (including 256 patients with GIST [treated at the recommended dose] from study DCC-2618-01-001 and study DCC-2618-03-001 (INVICTUS) and 95 were healthy subjects. The 114 GIST patients in the pivotal DCC-2618-03-001 study receiving ripretinib, comprises the 85 patients randomised to ripretinib up-front and the 29 patients in the placebo group that opted to switch to ripretinib in the open-label phase.

The size of the safety data base that is relevant to the applied indication i.e. treatment in GIST patients and who were exposed to the recommended dose [N=256], is considered sufficiently comprehensive to characterize the safety profile of ripretinib at least in the short term perspective given the rarity of the disease and the later line indication applied for.

DCC-2618-03-001 (INVICTUS)

Double-blind treatment period (ripretinib N=85; placebo N=43): The mean (SD) treatment duration for ripretinib was 24.44 (13.941) weeks as compared to the placebo arm (8.25 [6.757] weeks). Median treatment duration was similar with 23.86 weeks (range 1.3 to 59.4 weeks) and 6.00 weeks (range 0.4 to 38.4 weeks) for the ripretinib and placebo arms respectively.

A total of 45.9% received ripretinib for ≥ 6 months, 18.8% ≥ 9 months and 3.5% beyond 12 months.

Overall, 24.7% had any dose modification in the ripretinib arm and 20.9% in the placebo arm. In the ripretinib arm, 8.2% had any dose reduction, 21.2% had any dose interruption, and 3.5% had any dose increase. In the placebo arm, 2.3% had any dose reduction, 18.6% had any dose interruption with none having any dose increase.

It is noted that per protocol, dose escalation to 150 mg BID did not equal a dose increase. Dose increases occurred when returning to the prior dose after a dose reduction.

Mean (SD) relative dose intensity was 96.5 (7.62) in the ripretinib arm and 91.6 (11.96) in the placebo arm with a median of 100.0 (range 64 to 100) and 97.0 (range 56 to 100).

Open label treatment period: For the 29 patients who received placebo in the double-blind period and crossed over to receive ripretinib 150 mg QD in the open-label phase, the mean (SD) treatment was 16.87 (12.418) weeks with a median treatment duration of 12.00 weeks (range 1.0 to 44.1 weeks). A total of 24.1% had a treatment duration ≥ 6 months, 6.9 % ≥ 9 months and none beyond 12 months. Two patients (6.9 %) had any dose reduction whilst 31.0 % had any dose interruption. Mean (SD) relative dose intensity for these 29 patients was 92.5 (12.56) with a median of 100.0 (range 50 to 100).

For 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, the mean (SD) treatment was 5.23 (6.169) weeks and the median treatment duration was 3.86 (range 0.3 to 20.0) weeks. One patient (9.1%) had a treatment duration ≥ 3 months but none had a treatment duration that lasted beyond 6 months. These findings are not unexpected as patients continued into the open-label treatment period upon confirmed disease progression, remaining on the same dose that had already failed to sustain a tumour response in the double-blinded treatment period.

Of the 41 patients who dose escalated and received ripretinib 150 mg BID in the open-label period, the mean (SD) treatment was 14.79 (11.657) weeks and the median treatment duration 15.14 (range 0.1 to 43.1 weeks). Six (14.6%) patients had a treatment duration of ≥ 6 months but none beyond 12 months. Five (12.2%) patients had any dose reduction, and 11 (26.8%) patients had any dose interruption. Mean (SD) relative dose intensity for these 41 patients was 95.3 (9.92) with a median treatment duration of 100.0 (range 56 to 100). It is noted that the applicant does not propose any dose increases in the label.

The overall high relative dose intensity for ripretinib and the low number of patients requiring a dose reduction are considered indicative of a favourable tolerability. The proportion of dose interruptions does not raise any major concern.

Analysis Pools (Integrated Analysis)

The median time on treatment for patients in the pivotal study (Pool 1; N=114) and in the overall GIST subset treated at the recommended dose in Pool 2 (N=256) was 29.57 (range 1.0, 65.1) and 31.57

(range 0.4, 116.4), respectively. The corresponding means were 28.34 (14.934) and 35.92 (23.554), respectively.

The relative dose intensity in Pool 1 was median 100.00 % (range 64.3 to 100.0) with mean 95.03 (8.370) and 98.48 % (range 36.7 to 100.0) with mean 93.15 (11.591) for the GIST subset in Pool 2.

The fairly high rate of dose modifications is noted with 39.5 % in Pool 1 and 55.5 % in the GIST subset in Pool 2, the vast majority however, being interruptions (34.2 % and 39.8 % in the respective groups). Very few had a dose increase in Pool 1 (2.6 %) but 24.6 % in the GIST subset in Pool 2. At least one dose reduction was experienced by 12.3% and 14.5%, respectively.

For the GIST patients who received ripretinib 150 mg QD as ≥ 4th line of therapy (N=197), the mean (SD) duration of ripretinib treatment administration was 24.54 (18.258) weeks and a median of 21.86 (range 0.4 to 91.4) weeks. A total of 39.6% received ripretinib for ≥ 6 months, and 7.6% received treatment ≥ 12months.

The median (range) relative dose intensity administered was 100.0 % (46.7 to 103.0). A dose modification of any type was experienced by 44.2%, 9.1% had a dose reduction, and 25.9% experienced a dose interruption at any time.

At the updated cut-off date of **31 Aug 2019**, the median time on treatment had increased to about 9 months, similar in both Pool 1 and the GIST subset in Pool 2. The corresponding means were 33.24 (SD 19.147) and 42.93 (SD 31.386) weeks, respectively. Overall, 60.5% had a treatment duration ≥ 6 months, 43.0% ≥ 9 months, 18.4% ≥ 12 months but none beyond 2 years in Pool 1. In the GIST subset in Pool 2, the corresponding proportions were 61.7 %, 48.4%, 32.4% with 11 patients (4.3%) treated beyond 2 years. Data on relative dose intensity and dose modifications are overall in line with the observations at the previous respective data cut-off dates.

2.5.4.2. Adverse events

Methodology for determination of ADRs

For the ADR analysis, the double-blind period in Study DCC-2618-03-001 formed the primary basis of the determination of ADRs i.e. the TEAEs that were at least 5% higher in ripretinib arm as compared to the placebo arm and those that were at least 1.5 times greater in the ripretinib arm than those compared to placebo arm were considered ADRs. These include very common (10% and above) events of alopecia, fatigue, nausea, myalgia, constipation, diarrhoea, palmar-plantar erythrodysaesthesia syndrome, vomiting, weight decreased, muscle spasms, lipase increased, headache, dyspnoea, arthralgia, hypertension, dry skin, blood bilirubin increased, oedema peripheral, hypophosphataemia, and common (≥ 1% to <10%) events of pruritus, stomatitis, rash maculo-papular, hyperkeratosis, depression and dermatitis acneiform.

The ADRs were also evaluated across the pooled TEAE (all causality) safety population data (N=372, cut-off date: 31 Aug 2019). Risks were also reviewed to identify any potential ADRs and the risk of squamous cell carcinoma of skin (CMQ) was included.

The methodology for determination of ADRs is considered overall acceptable.

Study DCC-2618-03-001 (INVICTUS)

Summary of TEAEs in Double-Blind and Open-Label Periods (Safety Population)

Categories	Double-blind period			Open-label period		
	Placebo (N=43) n (%)	Ripretinib (N=85) n (%)	Total (N=128) n (%)	OL: Ripretinib 150 mg QD (originally received Placebo) (N=29) n (%)	OL: Ripretinib 150 mg QD (originally received Ripretinib) (N=11) n (%)	OL: Ripretinib 150 mg BID (N=41) n (%)
Any TEAE	42 (97.7)	84 (98.8)	126 (98.4)	28 (96.6)	11 (100)	39 (95.1)
Any Grade 3/4 TEAE	19 (44.2)	42 (49.4)	61 (47.7)	13 (44.8)	7 (63.6)	24 (58.5)
Any Treatment-emergent SAE	19 (44.2)	26 (30.6)	45 (35.2)	12 (41.4)	7 (63.6)	17 (41.5)
Any Drug-related TEAE	26 (60.5)	72 (84.7)	98 (76.6)	22 (75.9)	8 (72.7)	29 (70.7)
Any Grade 3/4 Drug-related TEAE	7 (16.3)	21 (24.7)	28 (21.9)	4 (13.8)	2 (18.2)	7 (17.1)
Any Drug-related Treatment-emergent SAE	3 (7.0)	8 (9.4)	11 (8.6)	0	1 (9.1)	4 (9.8)
Any TEAE Leading to Dose Reduction	1 (2.3)	6 (7.1)	7 (5.5)	2 (6.9)	0	1 (2.4)
Any TEAE Leading to Dose Interruption	9 (20.9)	20 (23.5)	29 (22.7)	10 (34.5)	5 (45.5)	15 (36.6)
Any TEAE Leading to Study Treatment Discontinuation	5 (11.6)	7 (8.2)	12 (9.4)	4 (13.8)	0	4 (9.8)
Any TEAE Leading to Death	10 (23.3)	5 (5.9)	15 (11.7)	5 (17.2)	4 (36.4)	7 (17.1)
Any Drug-related TEAE Leading to Dose Reduction	1 (2.3)	5 (5.9)	6 (4.7)	2 (6.9)	0	1 (2.4)
Any Drug-related TEAE Leading to Dose Interruption	3 (7.0)	12 (14.1)	15 (11.7)	3 (10.3)	2 (18.2)	7 (17.1)
Any Drug-related TEAE Leading to Study Treatment Discontinuation	1 (2.3)	4 (4.7)	5 (3.9)	0	0	1 (2.4)
Any Drug-related TEAE Leading to Death	1 (2.3)	1 (1.2)	2 (1.6)	-	-	-

Abbreviations: SAE=serious adverse event; TEAE=treatment-emergent adverse event
Note 1: Treatment-emergent adverse events are defined as any AE that occurs after administration of the first dose of study drug and through 30 days after the last dose of study drug.
Note 2: Drug-related adverse events are defined as those related or possibly related to study drug as assessed by the investigator.
Note 3: One treatment-emergent "FEVER" which misses severity grade was summarised as Grade 3 ("severe").
Note 4: TEAEs occurring during the double-blind treatment period are summarised by treatment arms. Incidences are based on the number of patients who initially received placebo or ripretinib 150 mg once daily (QD).
Note 5: This summary includes patients that entered the open-label period and received ripretinib 150 mg QD and/or ripretinib 150 mg BID, with 2 analysis sub-periods (Prior to- or Post- Intra-Patient Dose Escalation to ripretinib 150 mg BID). Data from a single patient on open-label QD whose dose escalated to open-label BID can be presented in each Period.
Note 6: Incidence rates are based on the number of patients who entered each sub-period.
Source: DCC-2618-03-001 CSR (13 Nov 2019) Table 31, Table 36.

Almost all patients experienced at least one TEAE during the double-blinded treatment period; 98.8% in the ripretinib arm vs 97.7% patients in the placebo arm. In the ripretinib arm, 49.4% patients

experienced a Grade 3/4 TEAE, 30.6% patients had a treatment-emergent SAE but only 7 patients (8.2%) had a TEAE leading to treatment discontinuation. A total of 7.1% experienced a TEAE leading to dose reduction, 23.5% a TEAE leading to dose interruption, and 5.9% a TEAE leading to death. In the placebo arm, 44.2% experienced a Grade 3/4 TEAE, 44.2% had a treatment-emergent SAE, 11.6% a TEAE leading to treatment discontinuation, 2.3% a TEAE leading to dose reduction, 20.9% a TEAE leading to dose interruption, and 23.3% a TEAE leading to death.

For the 41 patients who dose escalated and received ripretinib 150mg BID in the open-label period, TEAEs were reported in 95.1%, any Grade 3/4 TEAEs in 58.5%, and any TEAEs leading to dose interruption in 36.6%. TEAE leading to death were reported in 17.1%.

Overall, observations for the patients that continued on ripretinib 150 QD (N=11) and the group of patients that opted to cross over from placebo to ripretinib in the open label period (N=29) is in line with findings reported during the double-blinded treatment phase however any firm conclusion is hampered by the limited number of patients.

TEAEs

TEAEs Experienced in ≥ 10% Patients by PT in Double-blind and Open-Label Periods (Safety Population) -Study DCC-2618-03-001

	Double-blind period		Open-label period		
Preferred Term, n (%)	Placebo (N=43)	Ripretinib (N=85)	OL: Ripretinib 150 mg QD (originally received placebo) (N=29)	OL: Ripretinib 150 mg QD (originally received ripretinib) (N=11)	Ripretinib 150 mg BID (N=41)
Any Event	42 (97.7)	84 (98.8)	28 (96.6)	11 (100)	39 (95.1)
Alopecia	2 (4.7)	44 (51.8)	8 (27.6)	2 (18.2)	7 (17.1)
Fatigue	10 (23.3)	36 (42.4)	10 (34.5)	2 (18.2)	5 (12.2)
Nausea	5 (11.6)	33 (38.8)	4 (13.8)	1 (9.1)	8 (19.5)
Abdominal pain	13 (30.2)	31 (36.5)	8 (27.6)	3 (27.3)	10 (24.4)
Constipation	8 (18.6)	29 (34.1)	9 (31.0)	0	4 (9.8)
Myalgia	5 (11.6)	27 (31.8)	10 (34.5)	1 (9.1)	6 (14.6)
Diarrhoea	6 (14.0)	24 (28.2)	3 (10.3)	1 (9.1)	6 (14.6)
Decreased appetite	9 (20.9)	23 (27.1)	6 (20.7)	5 (45.5)	9 (22.0)
Palmar-plantar erythrodysaesthesia syndrome (PPES)	0	18 (21.2)	5 (17.2)	0	5 (12.2)
Vomiting	3 (7.0)	18 (21.2)	3 (10.3)	2 (18.2)	6 (14.6)
Weight decreased	5 (11.6)	16 (18.8)	6 (20.7)	2 (18.2)	7 (17.1)
Arthralgia	2 (4.7)	15 (17.6)	4 (13.8)	0	1 (2.4)
Blood bilirubin increased	0	14 (16.5)	0	0	6 (14.6)
Oedema peripheral	3 (7.0)	14 (16.5)	3 (10.3)	0	6 (14.6)
Muscle spasms	2 (4.7)	13 (15.3)	4 (13.8)	0	5 (12.2)
Anaemia	8 (18.6)	12 (14.1)	10 (34.5)	2 (18.2)	4 (9.8)
Hypertension	2 (4.7)	12 (14.1)	4 (13.8)	0	2 (4.9)
Asthenia	6 (14.0)	11 (12.9)	2 (6.9)	1 (9.1)	5 (12.2)
Dry skin	3 (7.0)	11 (12.9)	4 (13.8)	0	1 (2.4)
Headache	2 (4.7)	16 (18.8)	0	0	0
Dyspnoea	0	11 (12.9)	0	0	0
Hypophosphataemia	0	9 (10.6)	0	0	0
Lipase increased	0	9 (10.6)	0	0	0
Pruritus	2 (4.7)	9 (10.6)	0	0	0
Stomatitis	0	9 (10.6)	0	0	0

Preferred Term, n (%)	Double-blind period		Open-label period		
	Placebo (N=43)	Ripretinib (N=85)	OL: Ripretinib 150 mg QD (originally received placebo) (N=29)	OL: Ripretinib 150 mg QD (originally received ripretinib) (N=11)	Ripretinib 150 mg BID (N=41)
Insomnia	6 (14.0)	8 (9.4)	0	0	0
Dyspepsia	6 (14.0)	7 (8.2)	0	0	0
Abdominal distension	5 (11.6)	3 (3.5)	0	0	0
Death	0	0	4 (13.8)	3 (27.3)	5 (12.2)
Acute kidney injury	0	0	1 (3.4)	2 (18.2)	4 (9.8)
Gastrointestinal haemorrhage	0	0	0	1 (9.1)	5 (12.2)
Hyperkeratosis	0	0	3 (10.3)	0	2 (4.9)
Upper respiratory tract infection	0	0	4 (13.8)	0	2 (4.9)
Dehydration	0	0	3 (10.3)	0	1 (2.4)
Hyponatraemia	0	0	2 (6.9)	2 (18.2)	0
Urinary tract infection	0	0	3 (10.3)	0	1 (2.4)
Dizziness	0	0	3 (10.3)	0	0
Dyspnoea exertional	0	0	1 (3.4)	2 (18.2)	0
Hyperglycemia	0	0	3 (10.3)	0	0

Abbreviations: BID=twice daily; OL=open-label; QD=once daily.
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 summarised 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 (for the double-blind period) or who entered each sub-period (for the open-label period).
Note 5: Table cutoff based on either arm having ≥10% patients with an adverse event.
Note 6: This summary includes patients that entered the open-label period and received ripretinib 150 mg QD and/or ripretinib 150 mg BID, with 2 analysis sub-periods (Prior to- or Post- Intra-Patient Dose Escalation to ripretinib 150 mg BID). Data from a single patient on open-label QD whose dose escalated to open-label BID can be presented in each Period.
Note 7: In the open-label period, an AE was recorded if the start date of the respective was in the defined follow-up period; the severity grades changes were not compared to the preceding period
Source: DCC-2618-03-001 CSR (13 Nov 2019), Table 32 and Table 37.

During the double-blind treatment period the treatment arms are comparable in regard to any TEAE. TEAEs occurring in ≥ 20% of patients in the ripretinib arm included alopecia (51.8%), fatigue (42.4%), nausea (38.8%), abdominal pain (36.5%), constipation (34.1%), myalgia (31.85%), diarrhoea (28.2%), decreased appetite (27.1%), palmar-plantar dysaesthesia syndrome (21.2%), and vomiting (21.2%).

Corresponding proportions of TEAEs occurring in ≥ 20% of patients in the placebo arm were abdominal pain (30.2%), fatigue (23.3%), and decreased appetite (20.9%).

TEAEs by Severity

Grade 3/4 TEAEs Reported by ≥ 2 Patients by PT in Double-blind and Open-label Periods (Safety Population) -Study DCC-2618-03-001

Preferred Term, n (%)	Double-blind period		Open-label period		
	Placebo (N=43)	Ripretinib (N=85)	Ripretinib 150 mg QD (originally received Placebo) (N=29)	Ripretinib 150 mg QD (originally received ripretinib) (N=11)	Ripretinib 150 mg BID (N=41)
Any Grade 3/4 Event	19 (44.2)	42 (49.4)	13 (44.8)	7 (63.6)	24 (58.5)
Anaemia	6 (14.0)	8 (9.4)	6 (20.7)	1 (9.1)	2 (4.9)
Abdominal pain	2 (4.7)	6 (7.1)	2 (6.9)	1 (9.1)	2 (4.9)
Hypertension	0	6 (7.1)	0	0	0
Hypophosphataemia	0	4 (4.7)	0	0	2 (4.9)
Lipase increased	0	4 (4.7)	0	0	0
Blood alkaline phosphatase increased	1 (2.3)	3 (3.5)	0	0	0
Fatigue	1 (2.3)	3 (3.5)	3 (10.3)	0	1 (2.4)
Nausea	0	3 (3.5)	0	0	0
Vomiting	0	3 (3.5)	0	2 (18.2)	2 (4.9)
Acute kidney injury	1 (2.3)	2 (2.4)	1 (3.4)	1 (9.1)	2 (4.9)
Ascites	0	2 (2.4)	1 (3.4)	0	3 (7.3)
Aspartate aminotransferase increased	1 (2.3)	2 (2.4)	0	0	0
Dehydration	1 (2.3)	2 (2.4)	0	0	0
Urinary tract infection	1 (2.3)	2 (2.4)	0	0	0
Asthenia	2 (4.7)	1 (1.2)	0	0	0
GGT increased	2 (4.7)	1 (1.2)	0	0	0
Sepsis	2 (4.7)	1 (1.2)	0	0	0
Gastrointestinal haemorrhage	0	0	0	1 (9.1)	4 (9.8)
Decreased appetite	0	0	0	1 (9.1)	2 (4.9)
Pneumonia	0	0	0	0	3 (7.3)
Hyperglycemia	0	0	2 (6.9)	0	0

Abbreviation: GGT= Gamma-glutamyltransferase.
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 summarised by treatment arms.
Note 4: One treatment-emergent "FEVER" which misses severity grade is summarised as Grade 3 ("severe"). (Patient 302001)
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: DCC-2618-03-001 CSR (13 Nov 2019), Table 33 and Table 38.

During the double-blind period, 49.4% were reported to have any Grade 3/4 event in the ripretinib arm. The most commonly reported and experienced in ≥ 5% patients were anaemia (9.4%), and abdominal pain and hypertension (7.1% each). In the placebo arm, 44.2% patients experienced any Grade 3/4 event with anaemia most commonly reported (14.0%).

Analysis Pools (Integrated Analysis)

Summary of TEAEs for the Analysis Pools (Integrated Analysis - Safety Population)

Categories	Pool 1	Pool 2		Pool 3
	DCC-2618-03-001 Patients 150 mg QD (N=114) n (%)	GIST Patients 150 mg QD (N=256) n (%)	Non-GIST Patients 150 mg QD (N=39) n (%)	All Patients Any Dose (N=351) n (%)
Any TEAE	114 (100)	256 (100)	39 (100)	350 (99.7)
Any Grade 3/4 TEAE	72 (63.2)	162 (63.3)	24 (61.5)	222 (63.2)
Any Treatment-emergent SAE	52 (45.6)	123 (48.0)	16 (41.0)	170 (48.4)
Any Drug-related TEAE	102 (89.5)	243 (94.9)	34 (87.2)	328 (93.4)
Any Grade 3/4 Drug-related TEAE	33 (28.9)	85 (33.2)	14 (35.9)	117 (33.3)
Any Drug-related Treatment-emergent SAE	13 (11.4)	31 (12.1)	8 (20.5)	46 (13.1)
Any TEAE Leading to Dose Reduction	9 (7.9)	33 (12.9)	2 (5.1)	42 (12.0)
Any TEAE Leading to Drug Interruption	43 (37.7)	113 (44.1)	15 (38.5)	153 (43.6)
Any TEAE Leading to Drug Discontinuation	15 (13.2)	30 (11.7)	6 (15.4)	46 (13.1)
Any TEAE Leading to Death	21 (18.4)	37 (14.5)	4 (10.3)	49 (14.0)
Any Drug-Related TEAE Leading to Dose Reduction	8 (7.0)	30 (11.7)	2 (5.1)	39 (11.1)
Any Drug-Related TEAE Leading to Drug Interruption	24 (21.1)	65 (25.4)	9 (23.1)	89 (25.4)
Any Drug-Related TEAE Leading to Drug Discontinuation	5 (4.4)	11 (4.3)	4 (10.3)	17 (4.8)
Any Drug-Related TEAE Leading to Death	1 (0.9)	2 (0.8)	0	2 (0.6)

Abbreviations: GIST=gastrointestinal stromal tumour; TEAE=treatment-emergent adverse event; SAE=serious adverse event.
Note 1: 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 adverse event considered drug-related by the Investigator.
Note 2: Drug-related adverse events are defined as those definite, probable or possibly related to study drug as assessed by the Investigator. Any adverse event with missing relationship to study drug will be counted as related to study drug. Any adverse event with missing severity will be counted as Severe (Grade 3).
Note 3: Information about adverse events leading to dose reduction and dose interruption comes from the adverse event CRF pages.
Note 4: Non-GIST group includes patients with other advanced malignancies than GIST.
Data cutoff date for study DCC-2618-01-001: 01 Mar 2019.
Data cutoff date for study DCC-2618-03-001: 31 May 2019.
Source: Module 5.3.5.3, ISS Table 8.1.

Almost all patients experienced at least one TEAE. The proportions of any Grade 3/4 were similar in Pool 1 and the GIST subset in Pool 2 (about 63%). In terms of any treatment-emergent SAE similarity in reporting rates are also observed (45.6% and 48.0% respectively). Any TEAE leading to treatment discontinuation were reported in 13.2% and 11.7% respectively. Any TEAE leading to dose reduction were 7.9% and 12.9% respectively and TEAE leading to dose interruption 37.7% and 44.1%, respectively. Any TEAE leading to death were reported in 18.4% and 14.5% respectively.

The safety profile in regard to any TEAE, severity, SAEs and dose modifications reported in the GIST patients receiving 150 mg QD and who previously had received ≥ 4th lines of therapies are in line with that reported for the overall GIST subset.

Overall, data from the GIST subset (N=256) supports the findings as reported in the pivotal study.

TEAEs

Most Common (≥10%) AEs by PT and Analysis Pool (Integrated Analysis -Safety Population)

	Pool 1	Pool 2		Pool 3
Preferred Term	DCC-2618-03-001 Patients 150 mg QD (N=114) n (%)	GIST Patients 150 mg QD (N=256) n (%)	Non-GIST Patients 150 mg QD (N=39) n (%)	All Patients Any Dose (N=351) n (%)
Any Event	114 (100)	256 (100)	39 (100)	350 (99.7)
Alopecia	61 (53.5)	146 (57.0)	8 (20.5)	174 (49.6)
Fatigue	50 (43.9)	126 (49.2)	10 (25.6)	171 (48.7)
Nausea	44 (38.6)	107 (41.8)	8 (20.5)	134 (38.2)
Myalgia	41 (36.0)	108 (42.2)	5 (12.8)	127 (36.2)
Constipation	42 (36.8)	98 (38.3)	9 (23.1)	121 (34.5)
Decreased appetite	38 (33.3)	84 (32.8)	6 (15.4)	112 (31.9)
Palmar-plantar erythrodysaesthesia syndrome (PPES)	26 (22.8)	86 (33.6)	2 (5.1)	101 (28.8)
Abdominal pain	48 (42.1)	82 (32.0)	2 (5.1)	98 (27.9)
Diarrhoea	33 (28.9)	74 (28.9)	4 (10.3)	94 (26.8)
Weight decreased	25 (21.9)	62 (24.2)	4 (10.3)	83 (23.6)
Vomiting	27 (23.7)	61 (23.8)	9 (23.1)	82 (23.4)
Lipase increased	10 (8.8)	47 (18.4)	11 (28.2)	76 (21.7)
Muscle spasms	22 (19.3)	62 (24.2)	4 (10.3)	73 (20.8)
Anaemia	25 (21.9)	51 (19.9)	5 (12.8)	71 (20.2)
Arthralgia	20 (17.5)	52 (20.3)	3 (7.7)	64 (18.2)
Dyspnoea	16 (14.0)	43 (16.8)	4 (10.3)	63 (17.9)
Headache	20 (17.5)	52 (20.3)	6 (15.4)	63 (17.9)
Hypertension	18 (15.8)	46 (18.0)	1 (2.6)	59 (16.8)
Dry skin	16 (14.0)	45 (17.6)	2 (5.1)	55 (15.7)
Cough	9 (7.9)	33 (12.9)	2 (5.1)	48 (13.7)
Back pain	13 (11.4)	41 (16.0)	1 (2.6)	47 (13.4)

Preferred Term	Pool 1	Pool 2		Pool 3
	DCC-2618-03-001 Patients 150 mg QD (N=114) n (%)	GIST Patients 150 mg QD (N=256) n (%)	Non-GIST Patients 150 mg QD (N=39) n (%)	All Patients Any Dose (N=351) n (%)
Blood bilirubin increased	18 (15.8)	36 (14.1)	4 (10.3)	46 (13.1)
Dizziness	10 (8.8)	33 (12.9)	2 (5.1)	44 (12.5)
Hypokalaemia	10 (8.8)	30 (11.7)	2 (5.1)	42 (12.0)
Oedema peripheral	23 (20.2)	34 (13.3)	1 (2.6)	40 (11.4)
Hypophosphataemia	11 (9.6)	31 (12.1)	2 (5.1)	39 (11.1)
Rash	5 (4.4)	28 (10.9)	3 (7.7)	37 (10.5)
Actinic keratosis	7 (6.1)	26 (10.2)	2 (5.1)	35 (10.0)
Pain in extremity	12 (10.5)	30 (11.7)	2 (5.1)	35 (10.0)

Abbreviation: GIST=gastrointestinal stromal tumour.
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 adverse event considered as drug-related by the Investigator.
Note 3: Patients who have more than one adverse event per preferred term are counted only once for each term.
Note 4: Most common events are presented for ≥10% of the Pool 3 column.
Note 5: Non-GIST group includes patients with other advanced malignancies than GIST.
Data cutoff date for study DCC-2618-01-001: 01 Mar 2019.
Data cutoff date for study DCC-2618-03-001: 31 May 2019.
Source: Module 5.3.5.3, ISS Table 10.1.1

TEAEs reported in ≥ 25% of patients in Pool 1 were alopecia (53.5%), fatigue (43.9%), nausea (38.6%), myalgia (36.0%), constipation (36.8%), decreased appetite (33.3%), abdominal pain (42.1%), and diarrhoea (28.9%). PPES was reported in 22.8%.

The distribution and rates of TEAEs for the GIST subset are comparable. In the GIST subset in Pool 2 , the corresponding TEAEs ≥ 25% were alopecia (57.0%), fatigue (49.2%), nausea (41.8%), myalgia (42.2%), constipation (38.3%), decreased appetite (32.8%), abdominal pain (32.0%), diarrhoea (28.9%) and PPES 33.6%.

The overall safety profile in GIST patients previously having received ≥ 4th lines of therapies are in line with the safety profile reported for the overall GIST subset.

There was one case of Stevens-Johnson syndrome reported in the GIST subset in Pool 2 (Table 9.1.1). Upon further review however, a causal association between SJS and ripretinib cannot be established based on this case.

Lipase increased was reported in 8.8%, 18.4% and 21.7% in Pool 1, the GIST subset in Pool 2 and Pool 3, respectively. Furthermore, Grade 3/4 lipase increased was reported in 13.4 % in Pool 3. The clinical relevance of events of lipase increased remains unclear. The high reporting rate appears not to translate into an increased risk of pancreatitis.

In regard to phototoxicity, pre-clinical studies indicated that ripretinib has potential for photo-irritation/phototoxicity (information included in section 5.3 of the SmPC). In the Risk Analysis Population, 2 patients (1.0%, 2 of 197) experienced a photosensitivity reaction. No photosensitivity TEAEs were reported in patients treated with ripretinib in the double-blind period of the DCC-2618-03-001 study. It is however noted that as a pre-cautionary measure in this study, patients were instructed to avoid strong sunlight, sunlamps, and other sources of ultraviolet radiation for the duration of the

study in order to mitigate the potential risk of photo-irritation/phototoxicity. Moreover, prophylactic skin care was recommended which included sunscreen with SPF ≥ 30, hypoallergenic moisturizing creams or ointments for dry skin, and gentle skincare with fragrance-free soaps and detergents.

The applicant is asked to include a warning in section 4.4 about this risk and propose actionable measures to mitigate this event occurring in line with other TKIs in the same class. In addition, a causal association with ripretinib treatment should be further investigated and the applicant is asked to add `Phototoxicity´ as an important potential risk to the RMP and discuss how this risk should be further characterised.

TEAEs by severity

Most Common (>5%) Grade 3/4 TEAEs by PT and Analysis Pool (Integrated Analysis -Safety Population)

Preferred Term, n (%)	Pool 1	Pool 2		Pool 3
	DCC-2618-03-001 Patients 150 mg QD (N=114)	GIST Patients 150 mg QD (N=256)	Non-GIST Patients 150 mg QD (N=39)	All Patients Any Dose (N=351)
Any Grade 3/4 Event	72 (63.2)	162 (63.3)	24 (61.5)	222 (63.2)
Lipase increased	5 (4.4)	29 (11.3)	7 (17.9)	47 (13.4)
Anaemia	15 (13.2)	26 (10.2)	1 (2.6)	37 (10.5)
Hypertension	8 (7.0)	15 (5.9)	0	23 (6.6)
Abdominal pain	10 (8.8)	18 (7.0)	0	21 (6.0)

Abbreviation: GIST=gastrointestinal stromal tumour.
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 adverse event considered as drug-related by the Investigator.
Note 3: Patients who have more than one adverse event per preferred term are counted only once for each term.
Note 4: Most common events are presented for > 5% of the Pool 3 column.
Note 5: Non-GIST group includes patients with other advanced malignancies than GIST.
Data cutoff date for study DCC-2618-01-001: 01 Mar 2019.
Data cutoff date for study DCC-2618-03-001: 31 May 2019.
Source: Module 5.3.5.3, ISS Table 10.5.1.

In Pool 3, 63.2% reported at least one Grade 3 or 4 TEAE. Grade 3/4 TEAEs occurring in >5% of patients were lipase increased (13.4%), anaemia (10.5%), hypertension (6.6%), and abdominal pain (6.0%).

The overall safety profile regarding severity in GIST patients previously having received ≥ 4th lines of therapies, are in line with what have been reported for the overall GIST subset (Table not shown). Grade 3/4 TEAEs reported by >5% of patients included anaemia (8.6%), lipase increased (6.6%), and abdominal pain (5.1%).

Adverse events leading to dose modification

Dose reductions

At the cut-off date 31 May 2019, the frequency of dose reductions due to AEs was 12.0% in Pool 3 (N=351). The most commonly reported TEAEs leading to dose reduction were PPES (2.0%); lipase increased (1.4%); fatigue and non-cardiac chest pain (0.9% in each); and abdominal pain, nausea, pancreatitis, hyperbilirubinaemia, myalgia, memory impairment, and blood bilirubin increased (0.6%

each). All other TEAEs leading to dose reduction were reported by a maximum of one patient in all analysis pools (Table not shown).

The corresponding proportions for the GIST subset in Pool 2 (N=256), were PPES 2.7%; lipase increased 0.8%; fatigue 1.2%, non-cardiac chest pain 0.4%; and abdominal pain, pancreatitis, blood bilirubin increased and hyperbilirubinaemia 0.8% each, nausea and myalgia 0.4% each.

At the cut-off date 31 August 2019, the frequency of dose reductions due to AEs was 13.2% for Pool 3 (N=372) and 14.5% for the GIST subset in Pool 2 (N=256) with the distribution of TEAEs leading to dose reductions similar to that of the previous cut-off date.

Dose interruptions

A total of 43.6% of patients in Pool 3 reported at least one TEAE leading to dose interruption of ripretinib. The most commonly reported (occurring in >3% of total patients) included lipase increased (4.0%), abdominal pain and nausea (3.1% each), blood bilirubin increased (2.8%) and PPES (2.6%). Table included in the clinical AR.

AEs of clinical importance (AECIs)/AEs of special interest (AESIs)

Specific AEs were chosen based on their clinical importance, selected target-mediated effects, frequency in ripretinib clinical studies, experience with other TKIs, nonclinical findings, and after review of the safety findings from individual clinical studies. Categories of AECI included cardiac disorders, diarrhoea, myalgia and arthralgia, dermatological toxicity, and laboratory abnormalities. AESIs were defined per protocol, and included hyperbilirubinemia, blood bilirubin increased, squamous cell carcinoma of skin (SCC), keratoacanthoma, and actinic keratosis in DCC-2618-01-001, and SCC, keratoacanthoma, and actinic keratosis in INVICTUS. The analysis of AECI encompasses the protocol defined AESIs.

List of Adverse Events of Clinical Importance

Categories	Sub-Category	Search Strategy (MedDRA version 21.1)
Cardiac Disorder	Cardiac dysfunction	CMQ: PTs cardiac failure, acute left ventricular failure, diastolic dysfunction, and ventricular hypertrophy
	Hypertension	Hypertension (SMQ) (20000147) (Scope-Broad and Narrow)
Diarrhoea	Diarrhoea	Diarrhoea (excl infective) (10012736) (HLT), Gastrointestinal infections (10017966) (HLGT)
Myalgia and Arthralgia	Arthralgia	Arthralgia: Joint related signs and symptoms (10023226) (HLT)
	Myalgia	Myalgia: Muscle pains (10028323) (HLT)
Dermatological Toxicities	Palmar-plantar erythrodysaesthesia syndrome	PT- Palmar-plantar erythrodysaesthesia syndrome
	Alopecia	HLT - Alopecias (10001769)
	Squamous cell carcinoma of skin	CMQ: Squamous cell carcinoma, Squamous cell carcinoma of skin, Squamous cell carcinoma of head and neck, keratoacathoma
	Melanoma	CMQ- (PT- malignant melanoma, malignant melanoma in situ)
Lab Abnormalities	Hyperbilirubinaemia	Biliary disorders (SMQ) (20000118) (Scope-Broad and Narrow)

Abbreviations: CMQ=customized MedDRA query; HLT=high level term; HLGT=high level group term; SMQ=standardised MedDRA query; PT=preferred term.

TEAEs of Clinical Importance by SMQ/CMQ, Preferred Term, and Disease Group in Pool 3 (Safety Population)

SMQ/CMQ Category Preferred Term, n (%)	GIST (N=298)	Non-GIST (N=53)	Total (N=351)
Cardiac dysfunction	5 (1.7)	1 (1.9)	6 (1.7)
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)
Ventricular hypertrophy	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)
Diarrhoea	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)
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)
Palmar-plantar erythrodysaesthesia syndrome	98 (32.9)	3 (5.7)	101 (28.8)
Palmar-plantar erythrodysaesthesia syndrome	98 (32.9)	3 (5.7)	101 (28.8)
Alopecia	164 (55.0)	10 (18.9)	174 (49.6)

SMQ/CMQ Category Preferred Term, n (%)	GIST (N=298)	Non-GIST (N=53)	Total (N=351)
Alopecia	164 (55.0)	10 (18.9)	174 (49.6)
Squamous cell carcinoma of skin	25 (8.4)	3 (5.7)	28 (8.0)
Squamous cell carcinoma of skin	13 (4.4)	3 (5.7)	16 (4.6)
Squamous cell carcinoma of head and neck	8 (2.7)	0	8 (2.3)
Keratoacanthoma	6 (2.0)	1 (1.9)	7 (2.0)
Melanoma	3 (1.0)	0	3 (0.9)
Malignant melanoma in situ	2 (0.7)	0	2 (0.6)
Malignant melanoma	1 (0.3)	0	1 (0.3)
Hyperbilirubinaemia	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 tumour; MedDRA=Medical Dictionary for Regulatory Activities; SMQ=Standardised MedDRA queries; CMQ=customised 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 one adverse event per preferred term are counted only once in each term.
Data cutoff date for study DCC-2618-01-001: 01 Mar 2019.
Data cutoff date for study DCC-2618-03-001: 31 May 2019.
Source: Module 5.3.5.3; ISS Table 13.1.4.

AECIs reported in ≥ 25% of patients in Pool 3 were alopecia (49.6%), myalgia (36.2%), PPES (28.8%), and diarrhoea (26.8%). Twenty-eight (8.0%) patients experienced an event from the SMQ of SCC of skin; no patient had a TEAE of SCC of skin or SCC of head and neck that led to dose reduction or dose discontinuation.

Hypertension was reported in almost 20% of the safety population with Grade 3/4 reported in 6%. The proposed SmPC currently contains information on recommended dose modifications in 4.2, recommendations in 4.4 that ripretinib should not be initiated unless blood pressure is adequately controlled and in section 4.8. This is at this point considered adequate.

Alopecia is frequently reported with ripretinib treatment. A total of 55.0% of patients with GIST had at least one event of alopecia which led to dose reduction in one (0.3%) patient, and in dose interruption in one (0.3%) patient. None discontinued the study due to alopecia. `Alopecia´ is adequately reflected in section 4.8 of the SmPC.

Palmar-plantar erythrodysaesthesia syndrome (PPES) was reported in about 30% of patients. The SmPC currently contains information in sections 4.2 (recommendations on dose modifications according to severity), 4.4 and 4.8. This is considered adequate.

Cases of SCC of the skin occurred during ripretinib treatment. Three (0.9%) patients experienced an event from the SMQ of melanoma. Two (0.6%) patients had a TEAE of malignant melanoma in situ; neither of these events led to dose interruption, dose reduction, or dose discontinuation.

The SmPC currently contains information in section 4.4 stating that routine dermatologic examinations are recommended for patients taking ripretinib, and section 4.8. This is considered satisfactory.

Myalgia and arthralgia were other events considered expected with ripretinib treatment, reported in 36.2% and 18.2% of patients, respectively. In the proposed SmPC, myalgia and arthralgia are included in 4.2 (recommended dose modifications) and 4.8. This is at this point considered acceptable.

Diarrhoea was adjudicated as an AECI and reported in about 30% of the patients. It is recognised that although very commonly reported, the vast majority of events of diarrhoea was of Grade 1/2 and the majority of patients did not receive any treatment for diarrhoea. Furthermore, dose modifications were rarely required, and study drug was not withdrawn in any case.

The most frequently reported serious AECIs in Pool 3 were cardiac dysfunction (1.3%) whereof cardiac failure 0.8%; blood bilirubin increased (1.1%) and diarrhoea (0.5%). All other serious AECIs were reported in a single patient. The observations in Pool 3 are in line with the observations in the GIST subset (N=298).

2.5.4.3. Serious adverse events and deaths

Study DCC-2618-03-001 (INVICTUS)

Serious adverse events

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: Table 14.3.4.3.1.

In the ripretinib arm, 30.6% patients experienced any treatment-emergent SAE during the double-blind treatment phase. The most commonly reported in ≥ 2 patients were abdominal pain (4.7%), anaemia and death (3.5% each), nausea and vomiting (2.4% each). In the placebo arm, 44.2% patients experienced any treatment-emergent SAE with the most commonly reported being death

(9.3%), and abdominal pain, acute kidney injury, sepsis, and asthenia (4.7% each). It is noted that if the cause of death was unknown, Death NOS was to be entered as the description for the AE.

Deaths

Of the 25 patients who died during the double-blind and long-term follow-up periods, 22 died due to progression (11 patients in each arm). Five (5.9%) patients in the ripretinib arm and 10 (23.3%) patients in the placebo arm had TEAEs leading to death during study treatment or within 30 days of the last dose. In the ripretinib arm these were listed (MedDRA PTs) as hypoglycaemia, general physical health deterioration, and death (3 patients). In the placebo group TEAEs leading to death were acute kidney injury (2 patients), death (4 patients), septic shock and pulmonary oedema, asthenia, gastrointestinal perforation, and abdominal pain each in 1 patient.

All deaths that occurred during the open label and subsequent follow-up periods until 31 May 2019 in both treatment arms were due to disease progression except for one patient whose cause of death was unknown.

Analysis Pools (Integrated Analysis)

Most Common (≥ 1%) SAEs by PT and Analysis Pool (Integrated Analysis -Safety Population)

Preferred Term, n (%)	Pool 1	Pool 2		Pool 3
	DCC-2618-03-001 Patients 150 mg QD (N=114)	GIST Patients 150 mg QD (N=256)	Non-GIST Patients 150 mg QD (N=39)	All Patients Any Dose (N=351)
Any SAE	52 (45.6)	123 (48.0)	16 (41.0)	170 (48.4)
Death	15 (13.2)	24 (9.4)	2 (5.1)	29 (8.3)
Abdominal pain	7 (6.1)	15 (5.9)	0	18 (5.1)
Anaemia	4 (3.5)	5 (2.0)	1 (2.6)	9 (2.6)
Dyspnoea	1 (0.9)	4 (1.6)	2 (5.1)	8 (2.3)
Gastrointestinal haemorrhage	5 (4.4)	6 (2.3)	0	8 (2.3)
Sepsis	1 (0.9)	7 (2.7)	1 (2.6)	8 (2.3)
Urinary tract infection	3 (2.6)	5 (2.0)	1 (2.6)	8 (2.3)
Acute kidney injury	4 (3.5)	7 (2.7)	0	7 (2.0)
Tumour excision	0	4 (1.6)	0	7 (2.0)
Vomiting	5 (4.4)	5 (2.0)	0	7 (2.0)
Nausea	5 (4.4)	6 (2.3)	0	6 (1.7)
Ascites	3 (2.6)	5 (2.0)	0	5 (1.4)
Small intestinal obstruction	2 (1.8)	4 (1.6)	1 (2.6)	5 (1.4)
Blood bilirubin increased	1 (0.9)	2 (0.8)	1 (2.6)	4 (1.1)
Non-cardiac chest pain	0	2 (0.8)	0	4 (1.1)
Pneumonia	1 (0.9)	3 (1.2)	0	4 (1.1)

Abbreviations: GIST=gastrointestinal stromal tumour; MedDRA=Medical Dictionary for Regulatory Activities; SAE=serious adverse event.
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 adverse event considered as drug-related by the Investigator.
Note 3: Patients who have more than one adverse event per preferred term are counted only once for each term.
Note 4: Most common events are presented for ≥1% of the Pool 3 column.
Note 5: Non-GIST group includes patients with other advanced malignancies than GIST
Data cutoff date for study DCC-2618-01-001: 01 Mar 2019.
Data cutoff date for study DCC-2618-03-001: 31 May 2019.
Source: Module 5.3.5.3, ISS Table 10.2.1

SAEs were reported by 45.6% in Pool 1, 48.0% in Pool 2 (GIST subset) and 48.4% in Pool 3. SAEs occurring in >5% of patients were death (13.2% in Pool 1, 9.4% in Pool 2 [GIST patients] and 8.3% in Pool 3) and abdominal pain (6.1% in Pool 1, 5.9% in Pool 2 (GIST patients) and 5.1% in Pool 3).

Deaths in Study DCC-2618-01-001

At the 01 Mar 2019 cutoff, 35 patients had died (10 patients in the escalation Phase [whereof 8 GIST patients] and 25 patients during the Expansion Phase [whereof 19 patients with GIST]). The vast majority of the patients died of disease progression.

Laboratory findings

Haematology

In the GIST-population (N=298), the majority of patients did not experience any change from baseline (54 %, 80.9 %, 85.9 % and 85.9 % for Haemoglobin Decreased, Neutrophil Count Decreased, Platelet Count Decreased or White Blood Cell Decreased, respectively).

A total of 13.1 % experienced a worsening in neutrophil count decreased post-baseline. A Grade 3/4 worsening was observed in 1.7 %, and improvement from baseline in 4.0 %. Post-baseline worsening of platelet count decreased was observed in 11.1 %. No patient had worsening to Grade3/4 and improvement from baseline was seen in 1.0 %. A total of 31.9 % experienced a post-baseline worsening of haemoglobin decreased and 12.1 % had an improvement from baseline. A Grade 3/4 worsening was observed in 8.7 %.

Based on laboratory observations in regard to haematological parameters, ripretinib appears not to have any major bone marrow suppressive properties.

Liver Chemistry Parameters

In the GIST-population (N=298), no worsening or change from baseline was observed in the majority of patients. The respective proportions of patients without any change (increase) from baseline for ALP was 74.5%, ALT 82.9%, AST 72.5%, blood bilirubin 71.8% or serum amylase 75.5%.

A post-baseline worsening of ALT increase was observed in 11.7%; Grade 1 or 2 in 11.1%) and Grade 3/4, 0.7%. Improvement from baseline in alanine aminotransferase increased was seen in 3.0%. For AST increased, 21.1% experienced any worsening post-baseline of which 0.7% experienced a Grade 3/4. A total of 4.0% experienced an improvement from baseline. For blood bilirubin increased, any worsening was seen in 25.2%, with 1.7 % worsening to Grade 3 but no Grade 4. A total of 0.6% had an improvement from baseline.

A total of 20.8% experienced any worsening in serum amylase increased with the majority (19.5%) experiencing worsening to Grade 1 or 2.

Renal Chemistry Parameters

In the GIST-population (N=298), no worsening or change from baseline was observed in the majority of patients. A total of 44.0 % experienced a post-baseline worsening of lipase increased, that was Grade 1 or 2 in 27.5 %. Worsening lipase increased to Grade 3 was observed in 14.4 % and worsening to Grade 4 in 2.0 %. In regard to Albumin Decreased, a total of 19.1 % experienced a post-baseline worsening, that was Grade 1 or 2 in 17.8 %. Grade 3 was observed in 1.3 % with no Grade 4 reported.

Blood Pressure

A total of 77.5% of patients in Pool 3 (N=351) had a systolic BP within the normal range (<140 mmHg) at baseline, and 91.7% of patients had a diastolic BP within normal range (<90 mmHg) at baseline. A total of 43.9% in Pool 3 experienced no shift in post-baseline systolic BP during treatment, and 62.7% experienced no shift in post-baseline diastolic BP. A total of 3.4% of patients with systolic BP values within normal range at baseline had a post-baseline systolic BP ≥ 160mmHg, and 2.0% with normal diastolic BP at baseline had a post-baseline value ≥ 100mmHg.

It is noted that TEAEs of hypertension was reported in 16.8% of the patients in Pool 3. Of these, 6.6% experienced a Grade 3/4 TEAE. A TEAE of blood pressure increased was observed in 0.9%. It is further noted that 56.1% of the patients were reported to have hypertension in the medical history at baseline.

Left Ventricular Ejection Fraction

Left Ventricular Ejection Fraction at Baseline and Worst Post-baseline by Disease Group (Integrated Analysis –Pool3 –Safety Population)

LVEF (%)	GIST (N=298) n (%)	Non-GIST (N=53) n (%)	Total (N=351) n (%)
Baseline Value			
<50	0	0	0
≥50	298 (100)	53 (1000)	351 (100)
No Baseline Assessment	0	0	0
Worst Post-Baseline Value			
<50	9 (3.0)	1 (1.9)	10 (2.8)
≥50	231 (77.5)	22 (41.5)	253 (72.1)
No Post-Baseline Assessment	58 (19.5)	30 (56.6)	88 (25.1)

Abbreviations: GIST=gastrointestinal stromal tumour; LVEF=left ventricular ejection fraction;
Note 1: Baseline=The last non-missing value prior to receiving the first dose of ripretinib.
Note 2: Non-GIST group includes patients with other advanced malignancies than GIST
Data cutoff date for study DCC-2618-01-001: 01 Mar 2019.
Data cutoff date for study DCC-2618-03-001: 31 May 2019.
Source: Module 5.3.5.3[ISS Table 17.4. |

A baseline LVEF < 50% was an exclusion criterion in the pivotal study, hence the safety of ripretinib has not been assessed in this group of patients. It is however noted that very few had a LVEF < 50 as worst post-base-line value; 9 patients (3.0%) in the GIST subset. The proposed SmPC includes a recommendation for dose modifications in section 4.2, a recommendation on measures to be taken in 4.4 (stating that an assessment of LVEF should be performed prior to initiating ripretinib and during treatment if clinically indicated) and reflected in 4.8 (Description of selected adverse drug reactions). As a risk minimization measure, this is considered sufficient.

Effect on QT Prolongation/Torsade de Pointes

An AE analysis using the MedDRA SMQ "Torsade de pointes/QT Prolongation" and the preferred term "Seizure" by treatment and dose level was performed and based on this search, 18 cases were identified. The event term of these cases included syncope (5 cases); sudden death, seizure, and multiple organ dysfunction syndrome (3 cases each); and loss of consciousness, electrocardiogram QT prolonged, cardiac arrest, and ventricular arrhythmia (1 case each). Based on pre-clinical observations, ripretinib does not appear to have a negative effect in terms of QT prolongation.

Safety in special populations

Analyses of TEAEs and SAEs by age, gender, race, geographic region, and BMI for the analysis pools and by lines of therapies, has been provided. No safety concerns have been evoked based on these data, however a firm conclusion in regard to race and region is hampered by the small sample sizes for the non-white and non-US cohorts.

Paediatric Patients

The applicant submitted a product specific waiver request for all paediatric subsets which has been granted (EMA/PDCO/691681/201928, Feb 2020).

Elderly patients

MedDRA Terms, n (%)	Age <=65 (N=160, 62.3%)	Age 65-74 (N=66, 25.7%)	Age 75-84 (N=29, 11.3%)	Age 85+ (N=2, 0.8%)
Total AEs	160 (100.0)	66 (100.0)	29 (100.0)	2 (100.0)
Serious AEs – total	88 (55.0)	41 (62.1)	18 (62.1)	2 (100.0)
Fatal	27 (16.9)	14 (21.2)	5 (17.2)	1 (50.0)
Hospitalization/ prolong existing hospitalization	80 (50.0)	39 (59.1)	16 (55.2)	2 (100.0)
Life-threatening	17 (10.6)	5 (7.6)	2 (6.9)	0
Disability/incapacity	2 (1.3)	2 (3.0)	1 (3.4)	0
Other (medically significant)	11 (6.9)	7 (10.6)	3 (10.3)	0
AEs leading to treatment discontinuation	24 (15.0)	11 (16.7)	4 (13.8)	0
Psychiatric disorders (SOC)	53 (33.1)	15 (22.7)	7 (24.1)	2 (100.0)
Nervous system disorders (SOC)	98 (61.3)	37 (56.1)	14 (48.3)	2 (100.0)
Accidents and injuries	0	0	0	0
Cardiac disorders (SOC)	30 (18.8)	17 (25.8)	5 (17.2)	1 (50.0)
Vascular disorders (SOC)	53 (33.1)	25 (37.9)	12 (41.4)	0
Cerebrovascular disorders	0	0	0	0
Infections and infestations (SOC)	83 (51.9)	39 (59.1)	14 (48.3)	2 (100.0)
Anticholinergic syndrome (PT)	0 (–)	0 (–)	0 (–)	0 (–)
Quality of life decreased	NA	NA	NA	NA
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures (PTs)	34 (21.3)	14 (21.2)	7 (24.1)	1 (50.0)
Squamous cell carcinoma of skin (CMQ)	9 (5.6)	7 (10.6)	3 (10.3)	1 (50.0)
Actinic keratosis (PT)	16 (10.0)	8 (12.1)	7 (24.1)	0
Blood bilirubin increased (PT)	25 (15.6)	8 (12.1)	7 (24.1)	0
Hyperbilirubinemia (CMQ)	2 (1.3)	1 (1.5)	1 (3.4)	0
Lipase increased (PT)	27 (16.9)	13 (19.7)	8 (27.6)	0
Cardiac failure (SMQ)	39 (24.4)	13 (19.7)	6 (20.7)	1 (50.0)
Hypertension (PT)	36 (22.5)	13 (19.7)	7 (24.1)	0
Diarrhoea (PT)	60 (37.5)	24 (36.4)	13 (44.8)	0

MedDRA Terms, n (%)	Age <65 (N=160, 62.3%)	Age 65-74 (N=66, 25.7%)	Age 75-84 (N=29, 11.3%)	Age 85+ (N=2, 0.8%)
Diarrhoea haemorrhagic (PT)	0 (–)	0 (–)	0 (–)	0 (–)
Arthralgia (HLT)	40 (25.0)	13 (19.7)	9 (31.0)	0
Myalgia (PT)	80 (50.0)	29 (43.9)	9 (31.0)	0
Palmar-plantar erythrodysaesthesia syndrome (PT)	68 (42.5)	16 (24.2)	10 (34.5)	1 (50.0)
Alopecia (PT)	101 (63.1)	38 (57.6)	12 (41.4)	0
Melanoma (CMQ)	1 (0.6)	2 (3.0)	0	0
Photosensitivity reaction (PT)	3 (1.9)	0	0	0

CMQ = customized MedDRA query; HLT = higher level term; PT = preferred term; SMQ = standardized MedDRA query; SOC = system organ class
Source: Table Q1 15.2

As expected, a slightly higher reporting rate is recognised with increasing age in particular in regard to Serious AEs, in the SOCs of cardiac, vascular disorders and Infections/Infestations. However, a firm conclusion on the safety profiles in regard to Age groups 75-84 and >85 is hampered by the limited number of patients (N=29 and N=2 respectively). Overall, the safety profiles comparing Age group < 65 with ≥65 appears fairly similar. No concern is raised.

Immunological events

Not addressed in the dossier and not requested.

Safety related to drug-drug interactions and other interactions

Please refer to the Pharmacokinetics section.

2.5.4.4. Discontinuation due to AEs

DCC-2618-03-001 (INVICTUS)

In the ripretinib and placebo arm, TEAEs leading to treatment discontinuation were reported in 7 (8.2%) patients and 11.6%, respectively. TEAEs leading to treatment discontinuation amongst the ripretinib exposed patients included general physical health deterioration (2 [2.4%]), anaemia, cardiac failure, vomiting, death, and palmar-plantar dysaesthesia syndrome (1 [1.2%] patient each).

Analysis Pools (Integrated analysis)

The discontinuation rate due to AEs is comparable across all three pools and subsets, ranging from 11.7% in the GIST subset in Pool 2 to 15.4% in the Non-GIST subset. In Pool 3, the most commonly reported TEAEs leading to treatment discontinuation were abdominal pain, cardiac failure, and fatigue (0.9% each); and ileus, vomiting, general physical health deterioration, sepsis, and dyspnoea (0.6% each). This pattern of TEAEs is in line with observations in Pool 1 and Pool 2.

Overall similar proportions were observed in regard to treatment discontinuations due to TEAEs (by SOC and PT) reported in the ≥ 4th line of therapies pool.

From a 4th line GIST perspective (per the CSR), the discontinuation rate due to TEAEs is considered low and points to a favourable tolerability of ripretinib.

Post marketing experience

Qinlock (ripretinib) has marketing approval in the United States (May 2020), Canada (June 2020), Australia (July 2020) via FDA Project Orbis regulatory pathway, Hong Kong (March 2021), China mainland (March 2021) and Taiwan (July 2021) and Switzerland (October 2021).

2.5.5. Discussion on clinical safety

The integrated safety analysis include data from the pivotal study DCC-2618-03-001 (INVICTUS) and study DCC-2618-01-001 at the initial data cut-off dates of 31 May 2019 (date that the study was unblinded), and 01 Mar 2019, respectively. After the NDA submission in the US, an updated 90-day safety analysis was performed at the request of FDA with a cut-off date of 31 Aug 2019 and is included in the initial submission.

The integrated safety analysis includes three main components:

- **Pool 1** - Pivotal study DCC-2618-03-001 (INVICTUS);
- **Pool 2** - The 150 mg QD subset from studies DCC-2618 01-001 and DCC-2618-03-001;
- **Pool 3** - All patients from both studies.

The safety data base initially submitted encompasses a total of 446 patients who received at least one dose of ripretinib. Of these, 256 patients with GIST from study DCC-2618-01-001 and study DCC-2618-03-001, were treated at the recommended dose. The size of the safety data base in terms of GIST patients exposed at the recommended dose (relevant to the applied indication) is considered sufficiently comprehensive to characterize the safety profile in the short-term perspective given the rarity of the disease and the later line indication applied for.

An updated safety analysis with an additional 14 month for the pivotal study DCC-2618-03-001 (initial data cut-off date 31th of May 2019 has been submitted as requested (10th of August 2020 as data cut-off). It is concluded that the safety profile for ripretinib based on this updated analysis is in main consistent with the safety profile as characterized based on the initial safety data. No new safety concern has been evoked based on the available data. This conclusion is also considered applicable for the requested safety up-date for the GIST cohort in Pool 2.

Available US post-marketing data covering the 6-month period from 15 May 2020 to 31 Dec 2020 do not show any new alarming or worrisome signals.

Pivotal study DCC-2618-03-001 (INVICTUS)

Double-blind treatment period (ripretinib N=85; placebo N=43): The mean (SD) treatment duration for ripretinib was 24.44 (13.941) weeks as compared to the placebo arm (8.25 [6.757] weeks). Median treatment duration was 23.86 weeks (range 1.3 to 59.4 weeks) and 6.00 weeks (range 0.4 to 38.4 weeks), respectively.

A total of 45.9% received ripretinib for ≥ 6 months, 18.8% ≥ 9 months and 3.5% beyond 12 months.

Open label treatment period: Of the 29 patients who received placebo in the double-blind period and opted to cross over to ripretinib 150 mg QD in the open-label period, the treatment duration was shorter with mean (SD) treatment of 16.87 (12.418) weeks and median treatment duration of 12.00

weeks (range 1.0 to 44.1 weeks). A total of 24.1% had a treatment duration ≥ 6 months, 6.9 % ≥ 9 months and none beyond 12 months.

For 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, one patient (9.1%) had a treatment duration ≥ 3 months but none beyond 6 months.

Of the 41 patients who dose escalated and received ripretinib 150 mg BID in the open-label period, the mean (SD) treatment was 14.79 (11.657) weeks and the median treatment duration 15.14 (range 0.1 to 43.1 weeks). Six (14.6%) patients had a treatment duration of ≥ 6 months but none beyond 12 months.

There is overall, a high relative dose intensity for ripretinib indicating a favourable tolerability.

TEAEs: During the double-blind treatment period, TEAEs occurring in ≥ 20% of patients in the ripretinib arm included alopecia (51.8%), fatigue (42.4%), nausea (38.8%), abdominal pain (36.5%), constipation (34.1%), myalgia (31.85%), diarrhoea (28.2%), decreased appetite (27.1%), palmar-plantar dysaesthesia syndrome (21.2%), and vomiting (21.2%). Corresponding proportions of TEAEs in the placebo arm were abdominal pain (30.2%), fatigue (23.3%), and decreased appetite (20.9%).

By severity: A total of 49.4% were reported to have any Grade 3/4 event in the ripretinib arm. The most commonly reported and experienced in ≥ 5% patients were anaemia (9.4%), and abdominal pain and hypertension (7.1%) patients each). In the placebo arm, 44.2% patients experienced any Grade 3/4 event. The most commonly reported was anaemia (14.0%).

SAEs: 30.6% patients in the ripretinib arm experienced any treatment-emergent SAE during the double-blind period. The most commonly reported in ≥ 2 patients in the ripretinib arm were abdominal pain (4.7%), anaemia (3.5%]), death (3.5%), nausea (2.4%), and vomiting (2.4%). In the placebo arm, 44.2% patients experienced any treatment-emergent SAE with the most commonly reported being death (9.3%), and abdominal pain, acute kidney injury, sepsis, and asthenia (4.7% each).

Deaths: Of the 25 patients who died during the double-blind and long-term follow-up periods, 22 died due to progression (11 patients in each arm). Five (5.9%) patients in the ripretinib arm and 10 (23.3%) patients in the placebo arm had TEAEs leading to death during study treatment or within 30 days of the last dose. In the ripretinib arm these were listed (MedDRA PTs) as hypoglycaemia, general physical health deterioration, and death (3 patients). In the placebo group TEAEs leading to death were acute kidney injury (2 patients), death (4 patients), septic shock and pulmonary oedema, asthenia, gastrointestinal perforation, and abdominal pain each in 1 patient.

All deaths that occurred during the open label and subsequent follow-up periods until 31 May 2019 in both treatment arms were due to disease progression except for one patient whose cause of death was unknown.

Analysis Pools (Integrated Analysis)

Overall, observations in terms of relative dose intensity, mean/median time on treatment, pattern of TEAEs, by severity, SAEs and treatment discontinuations due to AEs in Pool 2 (GIST subset) and Pool 3 are consistent with the observations in the pivotal DCC-2618-03-001 study. At the updated cut-off date of 31 Aug 2019 (FDA requirement), the median time on treatment had increased to about 9 months, similar in both Pool 1 and the GIST subset in Pool 2. The corresponding means were 33.24 (SD 19.147) and 42.93 (SD 31.386) weeks, respectively. Overall, 60.5% had a treatment duration ≥ 6 months, 43.0% ≥ 9 months, 18.4% ≥ 12 months but none beyond 24 months in Pool 1. In the overall GIST subset treated at the recommended dose in Pool 2, the corresponding proportions were 61.7 %, 48.4%, 32.4% and 4.3 % treated beyond 24 months.

Discontinuations due to AEs: TEAEs leading to treatment discontinuation in Pool 3 (N=351) were reported in 13.1 % with the most commonly reported TEAEs being abdominal pain, cardiac failure, and fatigue (0.9% each); and ileus, vomiting, general physical health deterioration, sepsis, and dyspnoea (0.6% each). At the data cut-off date of 31 Aug 2019 (as per FDA request), the corresponding proportion of any event leading to treatment discontinuation was 15.6% in Pool 3 (N=372), 13.7% in the GIST subset in Pool 2 (N=256) and 13.2% in Pool 1 (N=114; 85 patients during the double-blind treatment period+29 patients in the placebo arm that opted to cross over to ripretinib in the open label treatment period).

From an 4th line GIST perspective (per the CSR), the discontinuation rate due to TEAEs is considered low and points to a favourable tolerability of ripretinib.

Any event leading to drug reduction at the data cut-off date of 31 Aug 2019 amounted to 13.2% in Pool 3, 14.5% in the GIST subset in Pool 2 and 9.6% in Pool 1. The corresponding proportions for drug interruptions were 46.8%, 48.4% and 41.2%, respectively.

In regard to patients with liver/renal impairment the safety profile appears to be consistent with that of the overall study population and no new safety concern has been identified. A phase 1 study (DCC-2618-01-004) is planned to assess ripretinib in patients with hepatic impairment, whilst the safety and tolerability of ripretinib is being evaluated in a cohort of patients with renal impairment in the ongoing study 2618-01-001. At this point there is no evidence supporting a causal association between ripretinib and acute kidney injury. The current proposals regarding these special populations in the product information are considered adequate.
From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.5.6. Conclusions on clinical safety

The distribution and proportions of TEAEs including by severity and SAEs is very similar between presented safety data pools. This is also the case when comparing with patients that had received ≥ 4 lines of therapy prior to ripretinib treatment as well as in comparison with the updated safety data requested by the FDA (adding yet another 3 months of follow up and an additional 21 patients). Furthermore, the safety profile of ripretinib as initially characterised has been confirmed by the updated safety analysis with data cut-off 10th of August 2020. No new safety concern has been evoked based on this safety update.

In conclusion, it is recognised that there are overall high report rates of TEAEs, Grade 3/4 events and SAEs. Reassuringly however, is the low rate of treatment discontinuations due to AEs and the low rate of patients that needed a dose reduction due to AEs. Taken together, this points to a favourable safety profile with manageable toxicity.

2.6. Risk Management Plan

Safety concerns

Table 7 Summary of the safety concerns

Summary of safety concerns	
Important identified risks	Palmar-plantar erythrodysaesthesia syndrome Hypertension Cardiac failure Squamous cell carcinoma of skin
Important potential risks	Embryo-foetal toxicity Phototoxicity
Missing information	Use in patients with moderate or severe hepatic impairment Use in patients with severe renal impairment

Pharmacovigilance plan

Table 8 Ongoing and planned additional pharmacovigilance activities

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 - Required additional pharmacovigilance activities				
Study DCC-2618-01-004 Phase 1, open-label study to evaluate the PK, safety, and tolerability of ripretinib in subjects with hepatic impairment compared to healthy control subjects. (Ongoing)	To investigate the impact of mild, moderate, and severe hepatic impairment on ripretinib PK. To assess the PK, safety, and tolerability of a single 50 mg dose of ripretinib in subjects with hepatic impairment compared to matched healthy subjects with normal hepatic function.	• Use in patients with moderate or severe hepatic impairment	Study start date:	September 2019
			PK results:	June 2022
			Study end date (LPO):	December 2021
			Study report:	June 2022

Risk minimisation measures

Table 9 Summary table of risk minimisation activities by safety concern

Safety concern	Risk minimisation measures
Palmar-plantar erythrodysaesthesia syndrome (Important identified risk)	Routine risk minimisation measures: • *Dose modifications for Grade 2 and Grade 3 PPES in SmPC Section 4.2* • *Treatment guidance in SmPC Section 4.4 and in package leaflet section 4* • *SmPC Section 4.8* • *Package leaflet section 4* • *Restricted medical prescription* Additional risk minimisation measures: • *None*
Hypertension (Important identified risk)	Routine risk minimisation measures: • *Dose modifications and medical management of Grade 3 hypertension and to permanently discontinue ripretinib for Grade 4 hypertension in SmPC Section 4.2* • *Warning on the actions to take in SmPC Section 4.4* • *SmPC Section 4.8* • *Package leaflet section 4* • *Restricted medical prescription* Additional risk minimisation measures: • *None*
Cardiac Failure (Important identified risk)	Routine risk minimisation measures: • *Guidance to discontinue ripretinib in case of Grade 3 or 4 left ventricular systolic dysfunction in SmPC Section 4.2 and 4.4* • *Warning to assess ejection fraction prior to initiating ripretinib and during treatment as clinically indicated in SmPC Section 4.4* • *SmPC Section 4.8* • *Package leaflet section 4* • *Restricted medical prescription* Additional risk minimisation measures: • *None*
Squamous cell carcinoma of skin (Important identified risk)	Routine risk minimisation measures: • *Warning for patients to receive dermatological examinations when initiating ripretinib and routinely during treatment and on the actions to take in SmPC Section 4.4 and in package leaflet section 4* • *Warning to manage suspicious skin lesions with excision and dermatopathological evaluation in SmPC section 4.4* • *SmPC Section 4.8* • *Package leaflet section 4* • *Restricted medical prescription* Additional risk minimisation measures: • *None*
Embryo-foetal toxicity (Important potential risk)	Routine risk minimisation measures: • *Recommendation to advise women to avoid pregnancy while taking ripretinib unless clearly necessary, to verify the pregnancy status prior to initiating ripretinib and during the treatment, and to use effective contraception during treatment (with a barrier method of contraception if systemic contraceptive steroids are used) for at least 1 week after the final dose in SmPC Section 4.4 and 4.6 and in package leaflet section 2* • *Information on non-clinical findings in SmPC Section 5.3* • *Restricted medical prescription*

Safety concern	Risk minimisation measures
	Additional risk minimisation measures: • *None*
Phototoxicity (Important potential risk)	Routine risk minimisation measures: • *Recommendation to patients to avoid or minimise exposure to direct sunlight, sunlamps, and other sources of ultraviolet radiation due to the risk of phototoxicity associated with ripretinib; and advise patients to use measures such as protective clothing (long sleeves and hat) and sunscreen with high SPF in SmPC Section 4.4 and in package leaflet section 2* • *Restricted medical prescription* Additional risk minimisation measures: • *None*
Use in patients with moderate or severe hepatic impairment (Missing information)	Routine risk minimisation measures: • *Information that pharmacokinetics and safety in patients with moderate or severe hepatic impairment have not been studied and that no dosing recommendation can be made in this subgroup in SmPC in Section 4.2 and 5.2 and in package leaflet section 3* • *Guidance to closely monitor the overall safety in patients with moderate and severe hepatic impairment in SmPC Section 4.2* • *Restricted medical prescription* Additional risk minimisation measures: • *None*
Use in patients with severe renal impairment (Missing information)	Routine risk minimisation measures: • *Information that only limited clinical data are available in patients with severe renal impairment (CLcr <30 mL/min) and that a recommended dose of ripretinib has not been established in patients with severe renal impairment in SmPC Section 4.2 and 5.2 and in package leaflet section 3* • *Restricted medical prescription* Additional risk minimisation measures: • *None*

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

2.7. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR

cycle with the international birth date (IBD). The IBD is 15.05.2020. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.8. New Active Substance

The applicant compared the structure of ripretinib with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers ripretinib to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Qinlock (ripretinib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The following indication is being sought:

Qinlock is indicated for the treatment of adult patients with advanced gastrointestinal stromal tumour (GIST) who have received prior treatment with three or more kinase inhibitors, including imatinib.

The recommended dose of ripretinib is 150 mg (3 tablets of 50 mg) taken orally QD.

Gastrointestinal stromal tumours, GISTs, are rare sarcoma, however, the most common malignant subepithelial lesions of the gastrointestinal tract. GISTs arises from the interstitial cells of Cajal and occurs throughout the gastrointestinal tract, primarily in older patients. GIST tumours are, when metastasized, mostly to the peritoneum and the liver, regarded as incurable. Mutational analysis has a predictive value for sensitivity to molecular-targeted therapy and also a prognostic value. Despite progress, with respect to targeted therapies, during the last decades, secondary mutations in KIT and PDGFRA (gain-of-function mutations in proto-oncogene proteins) genes, remains a challenge.

3.1.2. Available therapies and unmet medical need

Surgical resection is the first choice for resectable GISTs without metastasis; and administration of tyrosine kinase inhibitors such as imatinib (Glivec) is the primary approach for unresectable, metastatic, or recurrent GISTs. Sunitinib (Sutent, second-line tyrosine kinase inhibitor) and regorafenib (Stivarga, third line multi kinase inhibitor) can be used in advanced GISTs after treatment failure with imatinib. Recently, avapritinib (Ayvakyt) was authorized for GISTs carrying the PDGFRA D842V mutation. However, in the advanced setting, it is not possible to obtain a permanent cure by tyrosine kinase inhibitors. The median PFS decreases with each subsequent TKI, from 60% ORR and median PFS of 18-24 months with imatinib down to 5-7% ORR and median PFS of 5-6 months with regorafenib.

3.1.3. Main clinical studies

The applicant provided two studies to support the claimed indication, the Phase 3, pivotal study DCC-2618-03-001, and in addition supportive evidence is provided by the Dose-Response study DCC-2618-01-001

- Pivotal study DCC-2618-03-001*(data cut-off: 31 May 2019)*: ongoing, Phase 3, 2-arm, randomised (2:1), placebo controlled, double-blind, international, multicentre study comparing the efficacy of ripretinib 150 mg QD + BSC in GIST patients who had received previous treatments with at least 3 prior TKI therapies (imatinib, sunitinib, and regorafenib; 4L+ population, n=129).
- Dose-Response study DCC-2618-01-001 *(data cut-off of 01 March 2019)*: on-going Phase 1, first-in-human, dose-escalation, expansion, open-label study to evaluate the safety, tolerability, PK, PD and efficacy of ripretinib in GIST patients (receiving the RP2D of 150 mg QD ripretinib; dose-escalation period) as 2nd (n=31), 3rd (n=28), 4th (n=46) or ≥4th (n=83) line of therapy.

3.1.4. Favourable effects

Pivotal study DCC-2618-03-001 Ripretinib+BSC vs Placebo+BSC

- In the primary analysis population including patients having received at least three prior lines of therapy, PFS, for the ripretinib arm was 27.6 weeks (95% CI 20.0, 29.9) vs 4.1 weeks (95% CI 4.0, 7.3), HR 0.15 (0.09,0,25) stratified log-rank; p < ,0001 for the placebo arm. The subgroup analyses and the sensitivity analysis consistently favour the ripretinib arm. In the ripretinib arm 60% of the patients had a PFS event and in the placebo arm 84% of the patients had a PFS event. The PFS data are considered mature.
- ORR for the ripretinib arm was 9.4% vs 0% for the placebo arm, nominal p-value: 0,0504.
- OS for the ripretinib arm was 65.6 weeks (95% CI 53.6, 65.6) vs 28.6 weeks (95% CI 17.9, 50.4) not statistically significant due to the prespecified hierarchical alfa-spending plan.
- TTP for the ripretinib arm was 28.0 weeks (95% CI 20.0, 36.4) vs 4.1 weeks (95% CI 4.0, 7.6) for the placebo arm.
- DoR was analysed for the eight patients in PR; one patient progressed, one underwent salvage surgery and for the rest of the responding patients the median DoR was not reached at DCO.

Overall, consistent results were observed for the PP population and for the analyses based on investigator assessment. Consistent results were also demonstrated for the relevant subgroups analysed, i.e. by age, gender, race, region, baseline ECOG status and number of prior systemic anticancer therapies.

Updated efficacy data with DCO 10 Aug 2020, demonstrated continued efficacy with ripretinib for patients with advanced GIST with regard to key efficacy results for the double-blind period and crossover patients in the open-label period.

Dose-Response study DCC-2618-01-001

Supportive evidence, even if there are differences in patients' baseline characteristics, comes from the non-comparative DCC-2618-01-001 study, where ORR was 7.2% in the 83 patients that received ripretinib after at least three prior lines of therapy. In addition, ORR was 14.3% (median DoR not reached) in 28 third line patients (i.e. following imatinib + sunitinib failure or intolerance) included in that study.

3.1.5. Uncertainties and limitations about favourable effects

The size of the study (85 vs 44 patients) is limited, whereby efficacy in subgroups cannot be reliably assessed, and it cannot be certain that randomisation produces complete balance between arms regarding prognosis.

Since ORR, the key secondary endpoint, did not reach significance at a 0.05 significance level, and due to the hierarchical alfa spending strategy, the OS results are not type-1 error controlled.

A higher proportion of elderly patients (≥65 years old) was enroled in the placebo group 50% vs. 33% in the ripretinib treatment group, mostly driven by a higher portion of very elderly patients (10 (22.7%) vs. 8 (9.4%) patients ≥75 years in placebo and ripretinib, respectively).

Both the pivotal and the phase 1 study included provisions for escalating the dose of ripretinib from 150QD to 150BID in patients with progressive disease. The problem with the data provided by the applicant on this matter for, is that there is no randomised control group to which outcomes can be

compared and therefore, this does not isolate a drug effect. Furthermore, there are no objective responses to isolate drug effects.

The intra-patient comparison of PFS is subject to uncertainty. Data are not robust enough to support a claim for this treatment strategy in the SmPC.–

3.1.6. Unfavourable effects

The safety database (integrated safety analysis) include data from the pivotal study DCC-2618-03-001 (INVICTUS) and study DCC-2618-01-001 at the initial data cut-off dates of 31 May 2019 (date that the study was unblinded), and 01 Mar 2019, respectively. An updated 90-day safety analysis (requested by the FDA) with a cut-off date of 31 Aug 2019 adding data from 21 patients has also been submitted.

The integrated safety analysis includes three main components:

- **Pool 1** - DCC-2618-03-001 (INVICTUS); N=114 (85 patients from the double-blind period and 29 patients that crossed over from the placebo-arm to ripretinib in the open label phase;
- **Pool 2** - The 150 mg QD subset from studies DCC-2618 01-001 and DCC-2618-03-001; 256 patients with GIST and 39 non-GIST patients;
- **Pool 3** - All patients from both studies; N=351;

The size of the safety data base in terms of GIST patients exposed at the recommended dose (relevant to the applied indication) is considered sufficiently comprehensive to characterize the safety profile in the short-term perspective given the rarity of the disease and the later line indication applied for.

Pivotal study DCC-2618-03-001 (INVICTUS)

Double-blind treatment period (ripretinib N=85; placebo N=43): The mean and median treatment durations were similar; about 6 months for ripretinib treated patients and 2 months for patients in the placebo arm. A total of 45.9% received ripretinib for ≥ 6 months, 18.8% ≥ 9 months and 3.5% beyond 12 months.

Open label treatment period: For the 29 patients who received placebo in the double-blind period and opted to cross over to ripretinib 150 mg QD in the open-label phase, the treatment duration was shorter, about 4 months. A total of 24.1% had a treatment duration ≥ 6 months, 6.9 % ≥ 9 months and none beyond 12 months. A similar treatment duration was observed for the 41 patients who dose escalated and received ripretinib 150 mg BID in the open-label period. Six (14.6%) patients had a treatment duration of ≥ 6 months but none beyond 12 months. It is noted that the applicant is not proposing any dose increase options in the label.

TEAEs: During the double-blind treatment period, TEAEs occurring in ≥ 20% of patients in the ripretinib arm included alopecia (51.8%), fatigue (42.4%), nausea (38.8%), abdominal pain (36.5%), constipation (34.1%), myalgia (31.85%), diarrhoea (28.2%), decreased appetite (27.1%), palmar-plantar dysaesthesia syndrome (21.2%), and vomiting (21.2%).

By severity: A total of 49.4% were reported to have any Grade 3/4 event in the ripretinib arm. The most commonly reported and experienced in ≥ 5% patients were anaemia (9.4%), and abdominal pain and hypertension (7.1% each).

SAEs: A total of 30.6% in the ripretinib arm experienced any treatment-emergent SAE during the double-blind period. The most commonly reported in ≥ 2 patients in the ripretinib arm were abdominal pain (4.7%), anaemia (3.5%]), nausea (2.4%), and vomiting (2.4%).

Deaths: Of the 25 patients who died during the double-blind and long-term follow-up periods, 22 died due to progression (11 patients in each arm). Five (5.9%) patients in the ripretinib arm had TEAEs leading to death during study treatment or within 30 days of the last dose. These TEAEs are listed as hypoglycaemia (1 patient), general physical health deterioration (1 patient), and death (3 patients). All deaths occurring during the open label and subsequent follow-up periods until 31 May 2019 were due to disease progression, except for 1 patient whose cause of death was unknown.

Analysis Pools (Integrated Analysis)

Overall, observations in terms of relative dose intensity, mean/median time on treatment, pattern of TEAEs, by severity, SAEs and treatment discontinuations due to AEs in Pool 2 (GIST subset) and Pool 3 are generally consistent with the observations in DCC-2618-03-001 study/Pool 1. TEAEs leading to treatment discontinuation in Pool 3 were reported in 13.1 % with the most commonly being abdominal pain, cardiac failure, and fatigue (0.9% (3/351) of patients each); and ileus, vomiting, general physical health deterioration, sepsis, and dyspnoea (0.6% (2/351) of patients each). At the data cut-off date of 31 Aug 2019, the corresponding proportion was about 15% across pools. From a 4th line GIST perspective (per the CSR), the rates of discontinuations and dose reductions due to TEAEs are considered low and points to a favourable tolerability of ripretinib. The frequent dose interruptions are not of any major concern.

The safety profile of ripretinib as initially characterised has been confirmed by the requested updated safety analysis (data cut-off 10th of August 2020). No new safety concern has been identified based on the available data.

3.1.7. Uncertainties and limitations about unfavourable effects

- The size of the safety data base in terms of GIST patients exposed to the recommended dose (N=256) is limited.

3.1.8. Effects Table

*Table 10. **Effects Table for DCC-2618-03-001 study in ⩾ 4L GIST (DCO 01 Mar 2019)***

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
			Ripretinib 150 mg QD N= 85	Placebo N= 43	INVICTUS Study Double-Blind period	
PFS (Primary endpoint)	Median (95% CI)	weeks	27.6	4.1	HR; 0.15 (0.09,0,25) stratified log-rank; p < ,0001	
ORR (CR+PR) Difference in ORR (Key sec endpoint)	Median (95% CI)	%	8 (9.4) 9,4 (0.2,17.5)	0	nominal p-value: 0,0504 not statistically significant on a 5% level	

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
OS	Median (95% CI)	Weeks	65.6 (53.6, 65.6)	28.6 (17.9, 50.4)	HR 0,36* 95% CI (0.21, 0.62)	
TTP	Median (95% CI)	weeks	28.0 (20.0, 36.4)	4.1 (4.0, 7.6)		
Unfavourable Effects						
		%	Ripretinib 150 mg QD N= 85	Placebo N= 43	Invictus Study Double-Blind period	
TEAE ⩾10 % of patients	Any Alopecia Fatigue Nausea Abdominal pain Constipation Myalgia Diarrhoea PPE Vomiting Oedema periph Hypertension	%	98.8 51.8 42.4 38.8 36.5 34.1 31.8 28.2 0 7.0 7.0 4.7	97.7 4.7 23.3 11.6 30.2 18.6 11.6 14.0 21.2 21.2 16.5 14.1		
Grade 3/4	Any Anaemia Abdominal pain Hypertension Hypophosphatamia Lipase increase ALP increase Fatigue Nausea Vomiting AKI	%	49.4 9.4 7.1 7.1 4.7 4.7 3.5 3.5 3.5 3.5 2.4	44.2 14.0 4.7 0 0 0 2.3 2.3 0 0 2.3		
SAE (⩾2 patients by PT in DB period)	Any Abdominal pain Anaemia Nausea Vomiting AKI	%	30.6 4.7 3.5 2.4 2.4 1.2	44.2 4.7 2.3 0 0 4.7		
AE leading to dose reduction	Any Abdominal pain GI disorder PPE Arthritis	%	7.1 1.2 1.2 1.2 1.2	2.3 0 0 0 0		

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
TEAE leading to dose interrupt.	Any Nausea Bilirubin incr. PPE	%	23.5 3.5 2.4 2.4	20.9 0 0 0		
TEAE leading to discont.	Any Gen Health det. Anaemia Cardiac failure Vomiting PPE	%	8.2 2.4 1.2 1.2 1.2 1.2	11.6 0 0 0 0 0		

Abbreviations: PPE - Palmar-plantar erythrodysaesthesia syndrome
Notes:* Due to the multiple testing hierarchical testing procedure, OS results are not statistically significant.

Benefit-risk assessment and discussion

3.1.9. Importance of favourable and unfavourable effects

A statistically significant and numerically large PFS benefit was noted for the ripretinib arm compared to the control arm, best supportive care, which is deemed reasonably robust, notwithstanding the smallness of the pivotal trial, allowing imbalance between baseline factors. Updated efficacy data with DCO 10 Aug 2020, demonstrated continued efficacy. The demonstrated effect is deemed clinically relevant.

In terms of unfavourable effects, the overall high report rates in regard to TEAEs, Grade 3/4 events and SAEs are recognised. Reassuringly however, is the low rate of treatment discontinuations due to AEs and the low rate of patients that needed a dose reduction due to AEs which points to a favourable safety profile with manageable toxicity. The majority of deaths were due to disease progression and the number of deaths due to AEs does not raise any concern. The safety profile of ripretinib as initially characterised has been confirmed by the updated safety analysis with data cut-off 10th of August 2020. No new safety concern has been evoked based on this safety update.

3.1.10. Balance of benefits and risks

There are no major concerns. Efficacy has been established, and the safety profile is acceptable from a clinical point of view.

3.1.11. Conclusions

The overall benefit risk of Qinlock is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Qinlock is not similar to Ayvakyt within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Qinlock is favourable in the following indication:

Qinlock is indicated for the treatment of adult patients with advanced gastrointestinal stromal tumour (GIST) who have received prior treatment with three or more kinase inhibitors, including imatinib.

The CHMP therefore recommends the granting of the marketing authorisation to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that ripretinib is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

Paediatric Data

No significant studies in the agreed paediatric investigation plan *P/0122/2020* have been completed, in accordance with Article 45(3) of Regulation (EC) No 1901/2006, after the entry into force of that Regulation.