Summary Report of Benefit-Risk Assessment

QINLOCK TABLET 50 MG

NEW DRUG APPLICATION

Active Ingredient(s)	Ripretinib
Product Registrant	Specialised Therapeutics Asia Pte Ltd
Product Registration Number	SIN16769P
Application Route	Abridged evaluation
Date of Approval	28 April 2023

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A INTRODUCTION

Qinlock is indicated for the treatment of adult patients with advanced gastrointestinal stromal tumours (GIST) who have received prior treatment with 3 or more kinase inhibitors, including imatinib, sunitinib, and regorafenib.

The active substance, ripretinib, is a tyrosine kinase inhibitor (TKI) that inhibits KIT proto-oncogene receptor and platelet derived growth factor receptor alpha (PDGFRA) kinase implicated in proliferation, differentiation, and cell survival in gastrointestinal stromal tumours.

Qinlock is presented as white uncoated tablets containing 50 mg of ripretinib. Other ingredients in the tablet include crospovidone, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and silicon dioxide.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, ripretinib, is manufactured at Cambrex Charles City, Iowa, USA. The drug product, Qinlock Tablet 50 mg, is manufactured at Lonza Bend Inc, Oregon, USA.

Drug substance:
Adequate controls have been presented for the starting materials, intermediates, and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance is considered appropriate.

The characterisation of the drug substance and its impurities are appropriately performed. Potential and actual impurities are adequately controlled in accordance with ICH Q3A and Q3C guidelines.

The drug substance specifications are established in accordance with ICH Q6A and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods have been validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data presented was adequate to support the storage of the drug substance at 30°C with a re-test period of 36 months. Ripretinib is packaged in double linear low-density polyethylene (LLDPE) bags which are sealed with a crimp and placed inside a LLDPE sleeve and crimped. The bagged drug substance is then placed inside a high-density polyethylene (HDPE) drum.

Drug product:
As ripretinib has very low solubility at physiologic pH, an amorphous form of ripretinib was developed using spray drying technology to enhance its solubility and bioavailability. The spray-dried intermediate is then blended with the other excipients using a dry granulation approach before being compressed into tablets.

The manufacturing site is compliant with Good Manufacturing Practice (GMP). Proper development studies were conducted. There were differences between the clinical and commercial formulations, and a bioequivalence study was conducted which demonstrated bioequivalent between the clinical and commercial formulations. Process validation was

conducted on three production batches and the manufacturing process is demonstrated to be reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods have been validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted was adequate to support the approved shelf-life of 36 months when stored at or below 30ºC. The product is available in high-density polyethylene (HDPE) bottle closed with a white polypropylene child-resistant closure, supplied together with a PE canister containing silica gel. Each bottle contains 90 tablets.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of ripretinib in the treatment of advanced GIST was based on data from one pivotal study, INVICTUS (Study DCC-2618-03-001). This was a Phase 3, multicentre, randomised, double-blind, placebo-controlled study of ripretinib compared with placebo in patients with advanced GIST that had progressed on prior treatment with imatinib, sunitinib, and regorafenib. The study had two treatment periods: a double-blind treatment period and an open-label treatment period for patients with progressive disease who crossed over from placebo arm or those who continued assigned ripretinib treatment.

Patients in the double-blind treatment period of the study were randomised in a 2:1 ratio to receive oral ripretinib 150 mg once daily or matching placebo once daily, in combination with best supportive care. The randomisation was stratified by number of prior anticancer treatments (3 vs ≥4 prior treatments) and Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0 vs 1, or 2). Patients received treatment until they developed progressive disease, experienced unacceptable toxicity, or withdrew consent. Dose interruptions and/or reductions were allowed for unacceptable toxicity: the first dose level reduction to 100 mg once daily, and the second dose reduction to 50 mg once daily. As there is no treatment option for advanced GIST following progression on imatinib, sunitinib, and regorafenib, the comparison with placebo was considered acceptable.

The primary efficacy endpoint was progression-free survival (PFS) during the double-blind treatment period, defined as time from randomisation to documented disease progression per modified RECIST 1.1 or death due to any cause. The key secondary efficacy endpoint was objective response rate (ORR). Other secondary endpoints included overall survival (OS), time to response (TTR), duration of response (DOR) and quality of life measures. Data from blinded independent radiologic review (IRR) were used for the determination of PFS and ORR. The primary analysis was performed on the intent to treat (ITT) population. To control the type I error rate, the primary and secondary hypotheses were tested at alpha level of 0.05 in the following sequential order: PFS, ORR, OS, and quality of life. The study was ongoing at the time of review and the presented PFS and ORR information was based on data from the double-blind treatment period at data cut-off date of 31 May 2019.

A total of 129 patients were randomised in the study, comprising 85 patients in the ripretinib arm and 44 patients in the placebo arm. The mean age was 60.1 years (range: 29 to 83 years), 24.8% of the patients were aged 65 to 74 years and 14.0% were aged ≥75 years. The majority of patients in the overall study population were male (56.6%) and White (75.2%), and 7.0%

were Asian. The placebo arm had a higher percentage of male patients (59.1% vs 55.3%), Asian patients (11.4% vs 4.7%), patients aged ≥75 years (22.7% vs 9.4%), and patients with ECOG score 1 (54.5% vs 47.1%) as compared to the ripretinib arm. The most common tumour mutation was KIT exon 11 (58.1%) followed by KIT exon 9 (15.5%). A total of 10 patients (7.8%) had KIT and PDGFRA wild-type GIST. The majority of patients (62.8%) were treated with three prior systemic anticancer therapies, and 37.2% of patients with four or more prior systemic anticancer therapies. All patients had received prior treatment with imatinib, sunitinib and regorafenib. A total of 66.7% of patients had Stage IV disease while 15.5% had Stage III disease at initial diagnosis. The recruited patients were considered representative of the target patient population.

The primary analysis demonstrated statistically significant improvements in PFS based on IRR assessment for patients in the ripretinib arm compared to the placebo arm (hazard ratio [HR] 0.15; 95% CI: 0.09, 0.25; p<0.0001), with 85% reduction in the risk of progression or death. The median duration of PFS was 27.6 weeks in the ripretinib arm compared to 4.1 weeks in the placebo arm. The PFS results based on investigator's assessment (HR 0.19; 95% CI: 0.12, 0.32; p<0.0001) was consistent with the IRR assessment.

ORR based on IRR assessment was 9.4% in the ripretinib arm and 0% in the placebo arm. All responses observed in the ripretinib arm were confirmed partial responses. The difference in ORR between the treatment arms did not reach statistical significance (p=0.0504). The ORR based on the investigator's assessment was 10.6% for ripretinib and 0% for placebo. The median time to response in ripretinib arm was 8.1 weeks (range: 4.0 to 20.1 weeks), while the median duration of response was not reached.

During the double-blind treatment period, a trend for longer OS in the ripretinib arm was observed, with a HR of 0.36 (95% CI: 0.21, 0.62). At data cut-off date, the median OS was 65.6 weeks in the ripretinib arm and 28.6 weeks in the placebo arm. As statistical significance for ORR was not reached, the hypothesis testing for OS and quality of life was not formally performed in accordance with the pre-specified statistical sequential testing procedure.

Quality of life (QOL) as measured by the change from baseline in the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30 item (EORTC-QLQ-C30), EuroQol 5 Dimension 5 Level (EQ-5D-5L), and EQ-VAS favoured the ripretinib arm compared to the placebo arm.

Summary of Key Efficacy Results (Study INVICTUS)

	Ripretinib (N = 85)	**Placebo (N = 44)**
Primary endpoint		
PFS per IRR (ITT population)		
PFS events, n (%)	51 (60.0)	37 (84.1)
Median PFS (95% CI), weeks[d]	27.6 (20.0, 29.9)	4.1 (4.0, 7.3)
Hazard ratio[a] (95% CI)	0.15 (0.09, 0.25)	
Log-rank p-value	<0.0001[b]	
Key secondary endpoint		
ORR per IRR (ITT population), n (%)	8 (9.4)	0
Confirmed ORR, % (95% CI)	9.4 (4.2, 17.7)	0 (0.0, 8.0)
Fisher's exact test p-value	0.0504[c]	

	Ripretinib (N = 85)	Placebo (N = 44)
Median time to response (min, max), weeks	8.1 (4.0, 20.1)	-
Median duration of response (95% CI), weeks[d]	NE (16.0, NE)	NE (NE, NE)
Secondary endpoints		
OS events, n (%)	26 (30.6)	26 (59.1)
Median OS (95% CI), weeks[d]	65.6 (53.6, 65.6)	28.6 (17.9, 50.4)
Hazard ratio[a] (95% CI)	0.36 (0.21, 0.62)	

CI: confidence interval; IRR: independent radiological review; ITT: intention-to-treat; N: number of patients; n: number of patients with events; NE: not estimable; ORR: objective response rate; OS: overall survival; PFS: progression-free survival

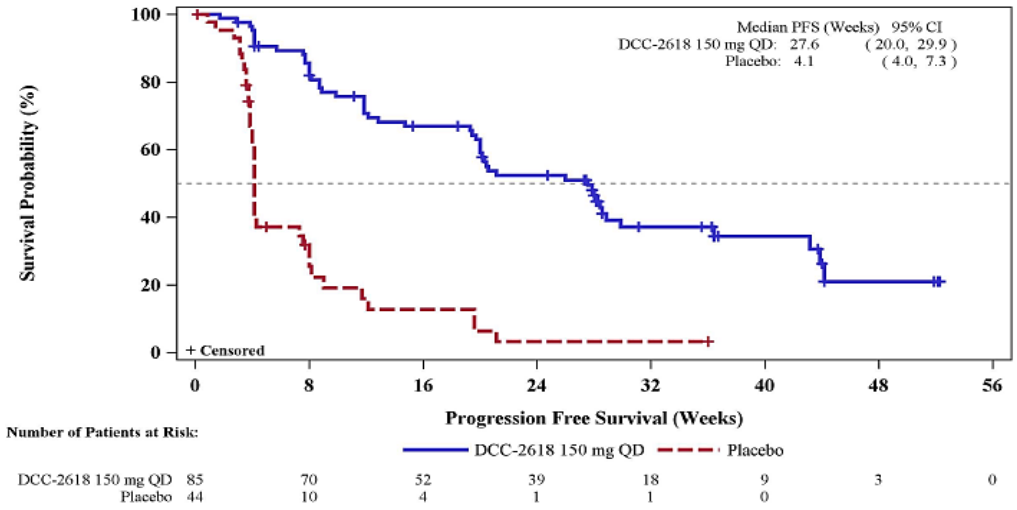
[a] Hazard ratio based on Cox proportional regression model that included treatment and randomization stratification factors as fixed factors.

[b] Statistical significance (2-sided) at the 0.05 level was reached.

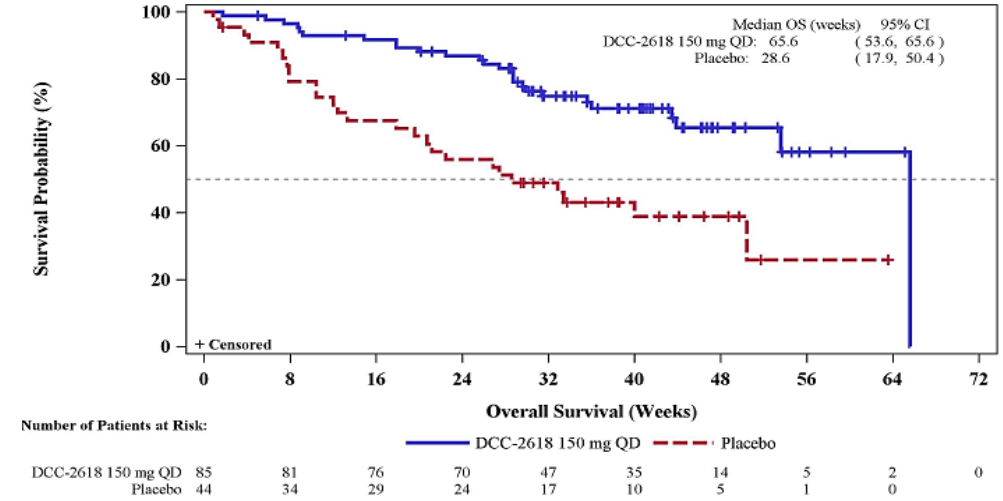
[c] Statistical significance (2-sided) at the 0.05 level was not reached.

[d] Median PFS, median duration of response, and median OS were estimated using Kaplan-Meier methods. Median time to response was estimated using the arithmetic median among patients with a confirmed response

Kaplan-Meier curves for Progression-free Survival based on independent radiologic review in Double-blind treatment period (Study INVICTUS)



Kaplan-Meier curves for Overall Survival (Study INVICTUS)



Pre-specified subgroup analyses demonstrated consistent treatment effect for the primary and key secondary endpoints across subgroups when stratified by age group (18 to 64 years, 65 to 74 years, 75 years or older), gender (male, female), race (White, non-White, not reported), country (USA, non-USA), ECOG performance status (0 vs 1 or 2), and number of prior systemic anti-cancer treatments (3 vs 4).

In terms of clinical efficacy, ripretinib demonstrated a robust improvement in median PFS and clinically meaningful improvement in OS in patients with advanced GIST in a fourth-line disease setting where no other therapeutic options currently available. The INVICTUS study results supported the efficacy of ripretinib in the treatment of adult patients with advanced GIST who have received prior treatment with imatinib, sunitinib, and regorafenib.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of ripretinib was based primarily on data derived from the Phase 3 INVICTUS study that comprised 128 patients who received at least one dose of study drug during the double-blind treatment period: 85 patients received ripretinib 150 mg QD and 43 patients received placebo. The median treatment duration was longer in the ripretinib arm (23.86 weeks) compared to the placebo arm (6.00 weeks).

During the double-blind period, 7 (8.2%) patients in the ripretinib arm had dose reduction, 18 (21.2%) patients had dose interruption, and 3 (3.5%) patients required dose increment. In the placebo arm, 1 (2.3%) patient had dose reduction, 8 (18.6%) patients had dose interruption, and none of the patients required dose increment. In the study, 11 of the 12 deaths in ripretinib arm and 11 of the 13 deaths in the placebo arm were due to disease progression. One patient in the ripretinib arm died during sleep with unknown reason.

Overall Safety Profile (Study INVICTUS, Safety Analysis Set)

Number (%) of patients with:	Ripretinib (N = 85)	Placebo (N = 43)
TEAE	84 (98.8)	42 (97.7)
Treatment-related TEAE	72 (84.7)	26 (60.5)
TEAE grade ≥3 in severity	42 (49.4)	19 (44.2)
Treatment-related TEAE grade ≥3 in severity	21 (24.7)	7 (16.3)
SAE	26 (30.6)	19 (44.2)
Treatment-related SAE	8 (9.4)	3 (7.0)
Deaths due to TEAE	5 (5.9)	10 (23.3)
Treatment-related death due to TEAE	1 (1.2)	1 (2.3)
Discontinuations due to TEAE	7 (8.2)	5 (11.6)
Treatment-related discontinuations due to TEAE	4 (4.7)	1 (2.3)
TEAE leading to dose interruption	20 (23.5)	9 (20.9)
Treatment-related TEAE leading to dose interruption	12 (14.1)	3 (7.0)
TEAE leading to dose reduction	6 (7.1)	1 (2.3)
Treatment-related TEAE leading to dose reduction	5 (5.9)	1 (2.3)

N: number of patients; SAE: serious adverse event; TEAE: treatment-emergent adverse event

Nearly all patients (98.8%) in the ripretinib arm experienced a treatment-emergent adverse event (TEAE). A higher percentage of patients in the ripretinib arm (84.7%) compared to the placebo arm (60.5%) reported treatment-related TEAEs. The types of TEAEs reported with

ripretinib were generally consistent with the known safety profile of KIT/PDGFRA tyrosine kinase inhibitors.

TEAEs related to study treatment that were reported more frequently in the ripretinib arm than the placebo arm were alopecia (49.4% vs 2.3%), myalgia (28.2% vs 9.3%), fatigue (25.9% vs 16.3%), nausea (25.9% vs 2.3%), diarrhoea (21.2% vs 7.0%), palmar-plantar erythrodysaesthesia syndrome (PPES) (21.2% vs 0%), constipation (15.3% vs 7.0%), decreased appetite (15.3% vs 7.0%), weight decreased (15.3% vs 7.0%), blood bilirubin increased (14.1% vs 0%), arthralgia (11.8% vs 0%) and muscle spasms (11.8% vs 4.7%).

Treatment-related grade 3 or 4 TEAEs that were reported more frequently in the ripretinib arm compared to the placebo arm were lipase increased (4.7% vs 0%), hypertension (3.5% vs 0%), and hypophosphatemia (2.4% vs 0%).

The rate of treatment-related SAE was higher in the ripretinib arm than the placebo arm (9.4% vs 7.0%) and those reported more frequently in the ripretinib arm were anaemia, cardiac failure, death, dyspnoea, faecaloma, gastroesophageal reflux disease, hypophosphatemia, nausea, and upper gastrointestinal haemorrhage (1 [1.2%] patient each in ripretinib arm versus none in placebo arm).

The TEAEs of special interest reported with ripretinib were PPES (21%), cutaneous squamous cell carcinoma (cuSCC) (4.7%), actinic keratosis (5.9%), hypertension (14%), cardiac failure (1.2%), and decreased ejection fraction (2.6%). These TEAEs of special interest were generally reported at similar incidence rates as other KIT/PDGFRA tyrosine kinase inhibitors, except for cuSCC which was observed to have a higher incidence with ripretinib. cuSCC could be related to BRAF inhibition by ripretinib as observed with other BRAF inhibitors. These safety concerns have been described in the relevant sections of the package insert including recommendations for dose interruptions, modifications and/or discontinuation, as well as warnings and precautions. These AEs will be monitored as part of routine pharmacovigilance.

In summary, the TEAEs observed with ripretinib were generally tolerable and manageable. The safety profile of ripretinib as fourth-line treatment in patients with advanced GIST was considered acceptable given the poor prognosis of the disease and limited treatment options.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Advanced gastrointestinal stromal tumour (GIST) is a rare, serious, and life-threatening disease. Despite good response to standard of care with surgical resection and treatment with TKIs, patients eventually progressed due to development of resistance to TKIs. There is an unmet medical need for treatment options in patients with advanced GIST who have progressed on prior TKI treatments.

The Phase 3 study, INVICTUS, demonstrated statistically significantly reduction in risk of disease progression or death (HR 0.15, 95% CI: 0.09, 0.25, p<0.0001) and improved median PFS (27.6 weeks vs 4.1 weeks) with ripretinib compared to placebo in patients with advanced GIST who had received prior treatment with imatinib, sunitinib, and regorafenib. With respect to the secondary endpoints, while the ORR with ripretinib treatment compared to placebo (9.4% vs 0%) was not statistically significant, the OS results suggested a trend for longer survival in the ripretinib arm (HR 0.36, 95% CI: 0.21, 0.62) with a median OS of 65.6 weeks compared to 28.6 weeks in the placebo arm.

The safety profile of ripretinib was considered acceptable relative to the effect size in terms of PFS and OS, considering the poor prognosis of advanced GIST and limited treatment options in the fourth-line treatment setting. The common adverse events with ripretinib including PPES, hypertension, nausea, constipation, diarrhoea, and myalgia can be managed through dose interruption, dose reduction and/or treatment discontinuation. These safety concerns have been adequately addressed in the package insert with relevant warnings and precautions as well as dose adjustment recommendations. The important identified risks with ripretinib including cuSCC, PPES, cardiac failure, and hypertension will be monitored as part of routine pharmacovigilance.

Overall, the benefit-risk profile of ripretinib was considered favourable in the treatment of adult patients with advanced GIST who have received prior treatment with 3 or more tyrosine kinase inhibitors, including imatinib, sunitinib, and regorafenib.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefits of ripretinib outweighed the risks in the treatment of adult patients with advanced gastrointestinal stromal tumours (GIST) who have received prior treatment with 3 or more kinase inhibitors, including imatinib, sunitinib, and regorafenib.

Approval of the product registration was granted on 28 April 2023.

APPROVED PACKAGE INSERT AT REGISTRATION

PRODUCT INFORMATION – QINLOCK® (ripretinib) TABLETS

1 NAME OF THE MEDICINE

Ripretinib

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each QINLOCK tablet contains 50 mg of ripretinib.

Ripretinib is a white to off-white crystalline solid. Ripretinib is a lipophilic, weak base compound, practically insoluble in aqueous media.

Excipients with known effect: lactose.

For the full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

QINLOCK tablets are white to off-white oval shaped tablets debossed with 'DC1' on one side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

The recommended dosage of QINLOCK is 150 mg (three 50 mg tablets) orally once daily with or without food until disease progression or unacceptable toxicity.

Instruct patients to swallow tablets whole.

Advise patients to take QINLOCK at the same time each day.

Advise patients to take a missed dose if less than 8 hours have passed since the missed scheduled dose.

Advise patients not to take an additional dose if vomiting occurs after taking QINLOCK and to continue with their next scheduled dose.

Dose modification guidelines

The recommended dose reduction for adverse reactions is:

- QINLOCK 100 mg orally once daily.

Permanently discontinue QINLOCK in patients who are unable to tolerate 100 mg orally once daily.

The recommended dosage modifications of QINLOCK for adverse reactions are provided in Table 1.

Table 1: Recommended Dose Modifications for QINLOCK

Adverse Reaction	**Severity[a]**	**Dosage Modifications**
Palmar-Plantar Erythrodysaesthesia Syndrome [PPES]) [see Section 4.4 Special Warnings and Precautions for Use]	Grade 2	• Withhold QINLOCK until Grade ≤1 or baseline. If recovered within 7 days, resume QINLOCK at same dose; otherwise, resume at reduced dose. • Consider re-escalating QINLOCK if maintained at Grade ≤1 or baseline for at least 28 days. • If PPES recurs, withhold QINLOCK until Grade ≤1 or baseline and then resume QINLOCK at a reduced dose regardless of time to improvement.
	Grade 3	• Withhold QINLOCK for at least 7 days or until Grade ≤1 or baseline (maximum 28 days). Resume QINLOCK at a reduced dose. • Consider re-escalating QINLOCK if maintained at Grade ≤1 or baseline for at least 28 days.
Hypertension [see Section 4.4 Special Warnings and Precautions for Use]	Grade 3	• If symptomatic, withhold QINLOCK until symptoms have resolved and blood pressure is controlled. • If blood pressure is controlled to Grade ≤1 or baseline, resume QINLOCK at the same dose; otherwise, resume QINLOCK at reduced dose. • If Grade 3 hypertension recurs, withhold QINLOCK until symptoms have resolved and blood pressure is controlled. Resume QINLOCK at a reduced dose.

Adverse Reaction	Severity[a]	Dosage Modifications
	Grade 4 Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis)	Permanently discontinue QINLOCK.
Left Ventricular Systolic Dysfunction [see Section 4.4 Special Warnings and Precautions for Use]	Grade 3 or 4	Permanently discontinue QINLOCK.
Arthralgia or Myalgia	Grade 2	• Withhold QINLOCK until Grade ≤1 or baseline. If recovered within 7 days, resume QINLOCK at same dose; otherwise, resume QINLOCK at reduced dose. • Consider re-escalating QINLOCK if maintained at Grade ≤1 or baseline for at least 28 days. • If arthralgia or myalgia recurs, withhold QINLOCK until Grade ≤1 or baseline and then resume QINLOCK at a reduced dose regardless of time to improvement.
	Grade 3	• Withhold QINLOCK for at least 7 days or until Grade ≤1 or baseline (maximum of 28 days). Resume QINLOCK at a reduced dose. • Consider re-escalating QINLOCK if maintained at Grade ≤1 or baseline for at least 28 days.
Other adverse reactions	Grade 3 or 4	• Withhold QINLOCK until Grade ≤1 or baseline (maximum 28 days), and then resume QINLOCK at a reduced dose; otherwise, permanently discontinue. • Consider re-escalating QINLOCK if no recurrence of the adverse reaction for at least 28 days.

Adverse Reaction	Severity[a]	Dosage Modifications
		• If Grade 3 or 4 recurs, permanently discontinue QINLOCK.

a. Graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.03).

Paediatrics

The safety and effectiveness of QINLOCK in paediatric patients have not been established.

Patients with renal impairment

No dose adjustment is recommended for patients with mild and moderate renal impairment [creatinine clearance (CrCl 30 to 89 mL/min estimated by Cockcroft-Gault)]. The pharmacokinetics and safety of QINLOCK in patients with severe renal impairment (CrCl 15 to 29 mL/min estimated by Cockcroft-Gault) have not been studied.

Patients with hepatic impairment

No dose adjustment is recommended in patients with mild hepatic impairment (total bilirubin ≤1 x ULN and AST > 1 x ULN, or total bilirubin 1.0 to 1.5 x ULN and any AST). The pharmacokinetics and safety of QINLOCK in patients with moderate to severe hepatic impairment (total bilirubin >1.5 x ULN, any AST) have not been studied.

Geriatrics

Of the 85 patients in INVICTUS who received QINLOCK 150 mg orally once daily, 24% were between 65 to 74 years of age and 9% were 75 years of age or older. Clinical studies of QINLOCK did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently from younger patients.

Dose Modifications for CYP3A Inducers

Avoid concomitant strong or moderate CYP3A inducers during QINLOCK treatment.

If a moderate CYP3A inducer cannot be avoided, increase the QINLOCK dosing frequency from the recommended dose of 150 mg once daily to 150 mg twice daily during the co-administration period. Monitor for clinical response and tolerability. If the concomitant moderate CYP3A inducer is discontinued, resume QINLOCK dosage back to 150 mg once daily 14 days after the discontinuation of the moderate CYP3A inducer [see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions].

4.3 CONTRAINDICATIONS

Use of QINLOCK is contraindicated in patients with hypersensitivity to ripretinib or to any other component of QINLOCK tablets.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Palmar-Plantar Erythrodysaesthesia Syndrome

In the double-blind period of a randomised, placebo-controlled phase 3 trial (INVICTUS), Grade 1-2 palmar-plantar erythrodysaesthesia syndrome (PPES) occurred in 21% of the 85 patients who received QINLOCK [see Section 4.8 Adverse Effects (Undesirable Effects)]. PPES led to dose discontinuation in 1.2% of patients, dose interruption in 2.4% of patients, and dose reduction in 1.2% of patients.

Based on severity, withhold QINLOCK and then resume at same or reduced dose [see Section 4.2 Dose and Method of Administration].

New Primary Cutaneous Malignancies

In INVICTUS, cutaneous squamous cell carcinoma (cuSCC) occurred in 4.7% of the 85 patients who received QINLOCK, with a median time to event of 4.6 months (range: 3.8 to 6 months). In the pooled safety population, cuSCC and keratoacanthoma occurred in 7% and 1.9% of 351 patients, respectively.

In INVICTUS, melanoma occurred in 2.4% of the 85 patients who received QINLOCK. In the pooled safety population, melanoma occurred in 0.9% of 351 patients.

Perform dermatologic evaluations when initiating QINLOCK and routinely during treatment. Manage suspicious skin lesions with excision and dermatopathologic evaluation. Continue QINLOCK at the same dose.

Hypertension

In INVICTUS, Grade 1-3 hypertension occurred in 14% of the 85 patients who received QINLOCK, including Grade 3 hypertension in 7% [see Section 4.8 Adverse Effects (Undesirable Effects)].

Do not initiate QINLOCK in patients with uncontrolled hypertension. Adequately control blood pressure prior to initiating QINLOCK. Monitor blood pressure as clinically indicated during treatment with QINLOCK and initiate or adjust antihypertensive therapy as appropriate.

Based on severity, withhold QINLOCK and then resume at same or reduced dose or permanently discontinue [see Section 4.2 Dose and Method of Administration].

Cardiac Dysfunction

In INVICTUS, cardiac failure occurred in 1.2% of the 85 patients who received QINLOCK. In the pooled safety population, cardiac dysfunction (including cardiac failure, acute left ventricular failure, diastolic dysfunction, and ventricular hypertrophy) occurred in 1.7% of 351 patients, including Grade 3 adverse reactions in 1.1%.

In INVICTUS, Grade 3 decreased ejection fraction occurred in 2.6% of the 77 patients who received QINLOCK and who had a baseline and at least one post-baseline echocardiogram. In the pooled safety population, Grade 3 decreased ejection fraction occurred in 3.4% of the

263 patients in the pooled safety population who received QINLOCK and who had a baseline and at least one post-baseline echocardiogram.

In INVICTUS, cardiac dysfunction led to dose discontinuation in 1.2% of the 85 patients who received QINLOCK. The safety of QINLOCK has not been assessed in patients with a baseline ejection fraction below 50%.

Assess ejection fraction by echocardiogram or MUGA scan prior to initiating QINLOCK and during treatment, as clinically indicated. Permanently discontinue QINLOCK for Grade 3 or 4 left ventricular systolic dysfunction [see Section 4.2 Dose and Method of Administration].

Risk of impaired wound healing

Impaired wound healing complications can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, QINLOCK has the potential to adversely affect wound healing.

Withhold QINLOCK for at least 1 week prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of QINLOCK after resolution of wound healing complications has not been established.

Phototoxicity

Ripretinib exhibits a potential for phototoxicity. It is recommended to advise 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. Patients should be instructed to use measures such as protective clothing (long sleeves and hat) and sunscreen with high sun protection factor (SPF).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Both ripretinib and its active metabolite DP-5439 are mainly cleared by CYP3A and are substrates of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).

Effects of other medicinal products on ripretinib

Effect of Strong CYP3A/P-gp Inhibitors: Coadministration of itraconazole (a strong CYP3A inhibitor and P-gp inhibitor) increased ripretinib C_{max} by 36% and $AUC_{0-\infty}$ by 99%. DP-5439 C_{max} was unchanged; $AUC_{0-\infty}$ increased by 99%. Strong CYP3A/P-gp inhibitors should be used with caution and patients should be monitored. Ingestion of grapefruit is not recommended.

Effect of Strong CYP3A Inducers: Coadministration of rifampicin (a strong CYP3A inducer) decreased ripretinib C_{max} by 18% and AUC_{∞} by 61% and also decreased DP-5439 AUC_{∞} by 57% with increased C_{max} by 37% [see Section 4.2 Dosage and Method of Administration].

Effect of moderate CYP3A Inducers: Coadministration of efavirenz (a moderate CYP3A inducer) was predicted to decrease ripretinib C_{max} by 24% and decrease $AUC_{0-\infty}$ by 56%. DP-5439 C_{max} was predicted to remain unchanged while $AUC_{0-\infty}$ decreased by 56% [see Section 4.2 Dosage and Method of Administration].

Avoid concomitant strong or moderate CYP3A inducers during QINLOCK treatment. If a moderate CYP3A inducer must be co-administered, increase the QINLOCK dosing frequency from the recommended dose of 150 mg once daily to 150 mg twice daily during the co-administration period. Monitor for clinical response and tolerability. If the concomitant moderate CYP3A inducer is discontinued, resume QINLOCK dosage back to 150 mg once daily 14 days after the discontinuation of the moderate CYP3A inducer [see Section 4.2 Dosage and Method of Administration].

Effect of Acid-Reducing Agents: Coadministration of pantoprazole (a proton pump inhibitor) did not affect exposure to ripretinib.

Drug transporter systems: Based on in vitro data, medicinal products that are inhibitors of BCRP (e.g. cyclosporine A, eltrombopag) should be used with caution in combination with QINLOCK, as increased plasma concentrations of ripretinib or DP-5439 may be possible.

Effect of ripretinib on other medicinal products

CYP isoform-selective substrates: *In vitro* studies suggested ripretinib may inhibit CYP2C8. QINLOCK is to be used with caution in combination with substrates of CYP2C8 (e.g. repaglinide, paclitaxel), as co-administration may lead to increased exposure of CYP2C8 substrates.

The in vivo net effect of inhibition of CYP3A4 in the intestine and systemic CYP3A4 induction is unknown. Caution is recommended when co-administering ripretinib with sensitive CYP3A4 substrates with a narrow therapeutic window (e.g. cyclosporine, tacrolimus) or that are mostly metabolised in the intestine (e.g. midazolam).

Ripretinib and DP-5439 induced CYP2B6 in vitro. Co-administration of ripretinib with CYP2B6 substrates with narrow therapeutic index (e.g. efavirenz) may lead to loss of their efficacy.

Ripretinib and DP-5439 down-regulated CYP1A2 in vitro. Co-administration of ripretinib with CYP1A2 substrates with narrow therapeutic index (e.g. tizanidine) may lead to increased concentrations and monitoring is recommended.

It is unknown whether ripretinib may reduce the effectiveness of systemically acting hormonal contraceptives, and therefore women using systemically acting hormonal contraceptives should add a barrier method.

Drug transporter systems: *In vitro* studies suggested ripretinib is an inhibitor of P-gp and BCRP. DP-5439 is a substrate for P-gp and BCRP. DP-5439 is an inhibitor of BCRP and Multidrug And Toxin Protein 1 (MATE-1).

Medicinal products that are P-gp substrates with narrow therapeutic indices (e.g. digoxin, dabigatran etexilate) should be used with caution in combination with QINLOCK due to the likelihood of increased plasma concentrations of these substrates.

QINLOCK is to be used with caution in combination with BCRP substrates (e.g. rosuvastatin, sulfasalazine and irinotecan) and MATE-1 substrates (e.g. metformin) as co-administration of

QINLOCK with BCRP and MATE-1 substrates may lead to an increase of their exposure. Clinical studies with BCRP or MATE-1 substrates have not been conducted.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Based on findings from animal studies, QINLOCK may impair fertility in males of reproductive potential. Decreased testis and epididymis weights, as well as atrophy of the testes and degeneration of the seminiferous epithelium were observed in male rats at exposure levels (AUC) similar to the human exposure at 150 mg once daily.

Use in pregnancy

Category D

There are no clinical data on the use of QINLOCK in pregnant women to inform a drug-associated risk of major birth defects and miscarriage.

Based on findings from animal studies, QINLOCK can cause embryo-fetal harm when administered to a pregnant woman. QINLOCK should not be used during pregnancy.

QINLOCK should not be used during pregnancy. In an embryo-fetal development study in which pregnant rats were administered daily doses of ripretinib during organogenesis, ripretinib was given from gestational days 6 through 18 at doses 1, 5, or 20 mg/kg/day. Dose-related malformations primarily associated with the cardiovascular and skeletal systems were observed at a dose of 20 mg/kg/day (approximately 0.4 times the human exposure at 150 mg once daily).

An increased incidence of anatomic variations, indicative of developmental toxicity, also occurred at 20 mg/kg/day. Variations included malpositioned carotid and subclavian artery origins, malpositioned subclavian artery, absent or elongated innominate artery, misshapen and nodulated ribs, bipartite, incompletely ossified, or unossified vertebral centra, small or misshapen vertebral arches, and reductions in ossified forelimb and hindlimb phalanges, hindlimb metatarsals, and caudal vertebrae were also observed at 20 mg/kg/day.

Verify the pregnancy status of females of reproductive potential prior to initiating QINLOCK. Advise female patients of reproductive potential to use effective contraception during treatment and for at least 1 week after the final dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for at least 1 week after the final dose.

Effects of ripretinib on contraceptive steroids have not been studied. A barrier method contraception should be added if systemic contraceptive steroids are used.

Use in lactation

There are no data regarding the presence of ripretinib or its metabolites in human milk or their effects on the breastfed infant or on milk production. Because of the potential for adverse

reactions in breastfed infants, advise women not to breastfeed during treatment with ripretinib and for at least 1 week after the final dose.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No data available.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

In the Phase 3 double-blind, randomised (2:1), placebo-controlled trial (INVICTUS), 129 study participants with a diagnosis of advanced GIST were randomised to QINLOCK (N=85) or placebo (N=44) [see Section 5.1 Pharmacodynamic Properties]. The data described in this section reflect the safety population (N=128) who had received at least one dose of QINLOCK (N=85) or placebo (N=43). One study participant who was randomised to the placebo arm did not receive placebo. The safety results from the double-blind treatment period of INVICTUS are described below.

The most common adverse events (≥20%) observed in patients treated with QINLOCK (all grades) were alopecia, fatigue, nausea, abdominal pain, constipation, myalgia, diarrhoea, decreased appetite, palmar-plantar erythrodysaesthesia syndrome (PPES), and vomiting (Table 2). The most common Grade 3 or 4 laboratory abnormalities were increased lipase and decreased phosphate (Table 3).

Serious adverse events occurred in 31% of patients who received QINLOCK. Serious adverse reactions that occurred in >2% of patients were abdominal pain (4.7%), anaemia (3.5%), nausea (2.4%), vomiting (2.4%). Serious adverse events considered to be drug-related were reported in one (1.2%) patient each: anaemia, cardiac failure, death, dyspnoea, faecaloma, gastroesophageal reflux disease, hyperkalaemia, hypophosphatemia, nausea, and upper gastrointestinal haemorrhage.

Tabulated list of adverse events

Table 2 summarises the most frequently reported treatment-emergent adverse events (TEAEs) in ≥10% of patients with advanced GIST who received QINLOCK in the double-blind treatment period of INVICTUS.

Table 2: Treatment-Emergent Adverse Events (TEAEs) Reported in ≥10% of Patients Who Received QINLOCK with a Difference Between Arms of >5% Compared to Placebo in INVICTUS

Treatment-Emergent Adverse Events	QINLOCK (N=85)		Placebo (N=43)	
	Grades 1-4 %	Grades 3-4 %	Grades 1-4 %	Grades 3-4 %
Skin and subcutaneous tissue				
Alopecia	52	0	4.7	0
Palmar-plantar erythrodysaesthesia syndrome	21	0	0	0
Dry skin	13	0	7	0
Pruritus	11	0	4.7	0
General				
Fatigue	42	3.5	23	2.3
Peripheral oedema	17	1.2	7	0
Asthenia	13	1.2	14	4.7
Gastrointestinal				
Nausea	39	3.5	12	0
Abdominal pain	36	7	30	4.7
Constipation	34	1.2	19	0
Diarrhoea	28	1.2	14	2.3
Vomiting	21	3.5	7	0
Stomatitis	11	0	0	0
Musculoskeletal and connective tissue				
Myalgia	32	1.2	12	0
Arthralgia	18	0	4.7	0
Muscle spasms	15	0	4.7	0
Metabolism and nutrition				
Decreased appetite	27	1.2	21	2.3
Investigations				
Decreased weight	19	0	12	0
Nervous system				
Headache	19	0	4.7	0
Vascular				
Hypertension	14	7	4.7	0
Respiratory, thoracic and mediastinal				
Dyspnoea	13	0	0	0

Table 3 summarises the most frequently reported treatment-emergent laboratory abnormalities in ≥10% of patients with advanced GIST who received QINLOCK in the double-blind treatment period of INVICTUS.

Table 3: Laboratory Abnormalities Reported in ≥10% of Patients Who Received QINLOCK in the Double-Blind Treatment Period of INVICTUS[a]

Laboratory Abnormality	QINLOCK[a] (N=85)		Placebo[a] (N=43)	
	Grades 1-4 %	Grades 3-4[b] %	Grades 1-4 %	Grades 3-4 %
Haematology				
Increased activated partial thromboplastin time	35	0	9	0
Increased INR	21	3.8	15	0
Decreased neutrophil count	10	0	2.5	0
Chemistry				
Increased lipase	32	7	13	8
Decreased phosphate	26	4.9	2.5	0
Increased triglycerides	26	2.4	23	0
Decreased calcium	23	0	8	0
Increased blood bilirubin	22	0	5	2.5
Increased CPK	21	1.2	10	0
Decreased sodium	17	2.4	10	2.5
Increased creatinine	16	0	18	0
Increased serum amylase	13	1.2	5	0
Increased ALT	12	1.2	5	0

CPK=creatine phosphokinase; INR=international normalised ratio; ALT=alanine aminotransferase

a. The denominator used to calculate the rate varied from 82 to 83 for QINLOCK and 34 to 40 for placebo based on the number of patients with a baseline value and at least one post-treatment value.

b. Only includes Grade 3 laboratory abnormalities.

Table 4: Dose Interruptions, Dose Reductions, and Treatment Discontinuations due to Adverse Reactions

Event	QINLOCK (N=85) %	Placebo (N=43) %
Dose interruption	23.5	20.9
Dose reduction	7.1	2.3
Treatment discontinuation	8.2	11.6

Other Adverse Reactions

Clinically relevant adverse reactions that occurred in <10% of patients in the pooled safety population included cardiac ischemic events (cardiac arrest, acute coronary syndrome, and myocardial infarction), which occurred in 1.1% of patients. Of these, cardiac arrest and myocardial infarction were reported as fatal adverse reactions.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at drugsafety-STA@stbiopharma.com.

4.9 OVERDOSE

There is no known specific antidote for QINLOCK overdose. In the event of suspected overdose, interrupt QINLOCK, undertake general supportive measures, and observe until clinical stabilisation.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Ripretinib is a tyrosine kinase inhibitor that inhibits KIT proto-oncogene receptor tyrosine kinase (KIT) and platelet derived growth factor receptor A (PDGFRA) kinase, including wild type, primary, and secondary mutations. Ripretinib also inhibits other kinases *in vitro*, such as PDGFRB, TIE2, VEGFR2, and BRAF.

Cardiac Electrophysiology

No large mean increase in QTc interval (i.e., >20 ms) was detected following treatment with QINLOCK at the recommended dose of 150 mg taken orally once daily.

Clinical trials

The efficacy of QINLOCK was evaluated in INVICTUS, an international, multi-centre, randomised (2:1), double-blind, placebo-controlled trial. Eligible patients had unresectable, locally advanced or metastatic gastrointestinal stromal tumour (GIST) and had received prior treatment with imatinib, sunitinib, and regorafenib. Randomisation was stratified by prior lines of therapy (3

versus ≥4) and Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1 or 2). Patients received QINLOCK 150 mg or placebo orally once daily until disease progression or unacceptable toxicity. Tumour response assessments were performed every 28 days through for the first 4 months and then every 56 days thereafter.

The major efficacy outcome measure was progression-free survival (PFS) based on disease assessment by blinded independent central review (BICR) using modified RECIST 1.1 criteria, 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. Additional efficacy outcome measures included objective response rate (ORR) by BICR and overall survival (OS). Patients randomised to receive placebo could be treated with QINLOCK at the time of disease progression.

A total of 129 patients were randomised, 85 to QINLOCK and 44 to placebo.

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 randomised to placebo switched to QINLOCK after disease progression.

Of the 129 (85 ripretinib and 44 placebo) samples evaluable for central testing in GIST patients who participated in the INVICTUS trial, the most common primary GIST mutation subgroup detected by baseline tumor tissue were in KIT exon 11 (Ripretinib: 47 (55%), Placebo: 28 (64%)) followed by KIT exon 9 (Ripretinib: 14 (17%), Placebo: 6 (14%)), and PDGFRA (Ripretinib: 3 (4%), Placebo: 0 (0%)). Based on only baseline tumor tissue biopsies, 10 patients were determined to have a KIT/PDGFRA wild type mutation.

Efficacy results from INVICTUS are summarised in Table 5.

Table 5. Efficacy Results of INVICTUS

	QINLOCK (N=85)	**Placebo (N=44)**
Progression-Free Survival (PFS)[a]		
Number of events (%)	51 (60)	37 (84)
Progressive disease	46 (54)	32 (73)
Deaths	5 (6)	5 (11)
Median PFS (months) (95% CI)	6.3 (4.6, 6.9)	1.0 (0.9, 1.7)
Hazard ratio (95% CI)[b]	0.15 (0.09, 0.25)	
p-value[c]	< 0.0001	

	QINLOCK (N=85)	Placebo (N=44)
Overall Response Rate (ORR)[a]		
Overall Response Rate (%)	9	0
(95%, CI)	(4.2, 18)	(0, 8)
p-value[d]	0.0504	
Overall Survival (OS)[e]		
Number of Deaths, N (%)	26 (31)	26 (59)
Median OS (months) (95% CI)[e]	15.1 (12.3, 15.1)	6.6 (4.1, 11.6)
Hazard Ratio (95% CI)[c]	0.36 (0.21, 0.62)	

BICR=Blinded Independent Central Review; CI=Confidence Interval

a. Assessed per BICR
b. Hazard ratio is based on Cox proportional hazards regression model. This model includes treatment and randomisation stratification factors as fixed factors.
c. p-value is based on 2-sided stratified Log Rank test.
d. Based on Fisher's exact test. The p-value is not statistically significant.
e. Not evaluated for statistical significance as a result of the sequential testing procedure for the secondary endpoints of ORR and OS.

Figure 1: Kaplan-Meier Curve of Progression-Free Survival in INVICTUS

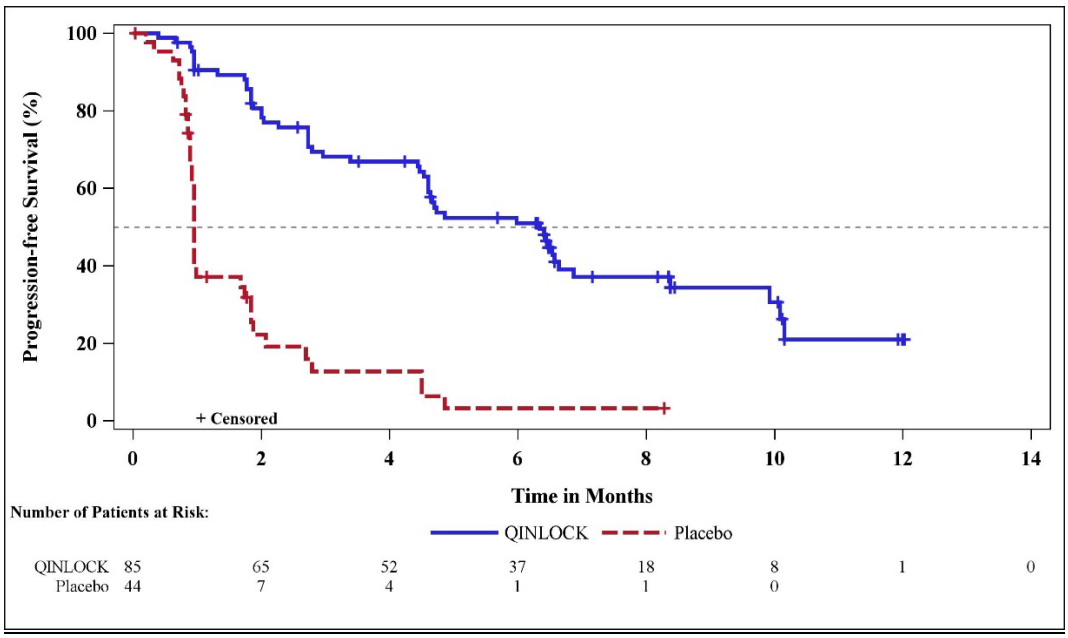
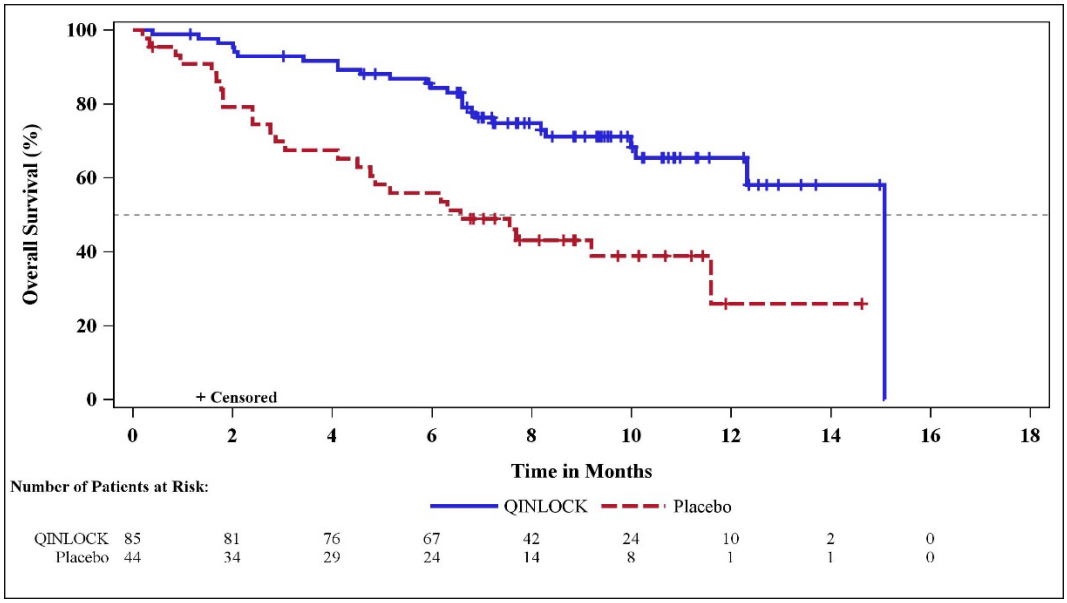


Figure 2: Kaplan-Meier Curve of Overall Survival in INVICTUS



5.2 PHARMACOKINETIC PROPERTIES

Absorption

Ripretinib reaches peak plasma concentrations at 4 hours after a single oral dose of 150 mg ripretinib (given as three tablets each containing 50 mg). The steady state $AUC_{0\text{-}12h}$ observed in patients at 150 mg is 5678 ng•h/mL. Steady state is achieved by approximately Day 15. Administration with a high-fat meal increased ripretinib $AUC_{0\text{-}24}$ and C_{max} by 30% and 22%, respectively. DP-5439 $AUC_{0\text{-}24}$ and C_{max} were higher by 47% and 66%, respectively.

Distribution

Both ripretinib and its active metabolite DP-5439 bind to plasma proteins at ≥ 99%. The apparent volume of distribution (Vss/F) is approximately 307 L.

Metabolism

Ripretinib was metabolised *in vitro*. CYP3A4/5 is the major metaboliser of ripretinib and its active metabolite, DP-5439, while CYP2C8 and CYP2D6 are only minor metabolisers.

Excretion

Following oral administration of ripretinib 150 mg once daily, the mean apparent oral clearance (CL/F) of ripretinib and DP-5439 at steady-state were 15.3 L/hr and 17.5 L/hr, respectively. The mean plasma elimination half-life was 14.8 hours and 17.8 hours for ripretinib and DP-5439, respectively.

In preclinical species, ^{14}C-labeled ripretinib dosed to Sprague-Dawley rats (oral) and beagle dogs (intravenous [iv]), resulted in greater than 87% of the radioactive dose being excreted in faeces and 1.8% or less in the urine.

PK analyses obtained from urine and faeces samples in 10 healthy volunteers showed that systemic elimination of ripretinib was not primarily attributed to the kidney. Through 1 week (168 hours) after a single oral administration of 50 mg ripretinib (given alone), 0.02% of the ripretinib dose was excreted as ripretinib in urine and 34.2% of the ripretinib dose was excreted as ripretinib in faeces.

Dose proportionality

In patients with advanced malignancies, ripretinib $AUC_{0\text{-}24h}$ increased approximately proportionally over a dose range of 20-250 mg (0.13 to 1.67 times the recommended dose), but C_{max} was slightly less than dose proportional; DP-5439 C_{max} and $AUC_{0\text{-}24h}$ were less than dose proportional within the dose range of 50-250 mg (0.33 to 1.67 times the recommended dose).

Pharmacokinetics in special patient populations

Population pharmacokinetic analyses of demographic data indicate that no clinically meaningful differences in the pharmacokinetics 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 estimated by Cockcroft-Gault) and mild hepatic impairment (total bilirubin ≤ULN and AST >ULN or total bilirubin 1 to 1.5 × ULN and any AST). The effects of severe renal impairment (CrCl 15 to 29 mL/min) or moderate to severe hepatic impairment (total bilirubin >1.5 × ULN, any AST) on the pharmacokinetics of ripretinib have not been studied.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Ripretinib was not mutagenic in an *in vitro* bacterial reverse mutation (Ames) assay or clastogenic in an *in vivo* rat bone marrow micronucleus assay. Ripretinib was weakly positive in an *in vitro* clastogenicity assay in human lymphocytes without metabolic activation. Ripretinib's active metabolite (DP-5439) was not mutagenic in an *in vitro* bacterial reverse mutation test or clastogenic in an *in vitro* chromosomal aberration assay in isolated human lymphocytes. Ripretinib is not expected to pose a genotoxic risk.

Carcinogenicity

Carcinogenicity studies have not been conducted with ripretinib.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each QINLOCK tablet contains the following inactive ingredients:

- crospovidone;
- hypromellose acetate succinate;
- lactose monohydrate;
- magnesium stearate;
- microcrystalline cellulose;
- silicon dioxide.

6.2 INCOMPATIBILITIES

No incompatibilities have been identified.

6.3 SHELF LIFE

The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C in the original package and keep the bottle tightly closed in order to protect from light and moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

QINLOCK 50 mg tablets are packaged with silica gel desiccant into white high-density polyethylene (HDPE) bottles. The bottles are closed with polypropylene child resistant closures with a polyethylene-faced induction heat seal liner. Each HDPE bottle contains 90 tablets.

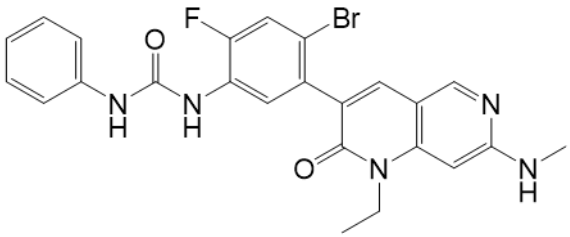
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical structure of ripretinib is shown below:



Chemical name: 1-(4-bromo-5-[1-ethyl-7-(methylamino)-2-oxo-1,2-dihydro-1,6-naphthyridin-3-yl]-2-fluorophenyl)-3-phenylurea

Molecular Formula: $C_{24}H_{21}BrFN_5O_2$

Molecular Weight: 510.36 g/mol

CAS number

1442472-39-0

7 PRODUCT REGISTRANT

Specialised Therapeutics Asia Pte Ltd
1 Harbourfront Avenue,
Keppel Bay Tower, #14-03/07,
Singapore 098632.

8 DATE OF FIRST APPROVAL

9 DATE OF REVISION

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information