Physician Prescribing Information

NAME OF MEDICINAL PRODUCT

QINLOCK 50 mg tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg of Ripretinib

Excipients with known effect

Each tablet contains 179 mg of lactose monohydrate (*see section Description (11)*).

For the full list of excipients, *see Description (11)*.

1 THERAPEUTIC INDICATION

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of QINLOCK is 150 mg 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.

2.2 Dosage Modifications for Adverse Reactions

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 Dosage Modifications for QINLOCK for Adverse Reactions

Adverse Reaction	Severity[a]	QINLOCK Dosage Modifications
Palmar-Plantar Erythrodysesthesia Syndrome (PPES) *[see Warnings and Precautions (5.1)]*	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 Warnings and Precautions (5.3)]*	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.
	Grade 4	Permanently discontinue QINLOCK.
Left Ventricular Systolic Dysfunction *[see Warnings and Precautions (5.4)]*	Grade 3 or 4	Permanently discontinue QINLOCK.
Arthralgia or Myalgia *[see Adverse Reactions (6.1)]*	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 *[see Adverse Reactions (6.1)]*	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. • If Grade 3 or 4 recurs, permanently discontinue QINLOCK.

[a] Graded per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (NCI CTCAE v4.03).

2.3 Dose Modifications for Moderate CYP3A Inducers

Avoid concomitant use of 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 Drug Interactions (7.1) and Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

Tablets: 50 mg, white to off-white, oval shaped, debossed with “DC1” on one side.

4 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 11.

5 WARNINGS AND PRECAUTIONS

5.1 Palmar-Plantar Erythrodysesthesia Syndrome

In INVICTUS, Grade 1-2 palmar-plantar erythrodysesthesia syndrome (PPES) occurred in 21% of the 85 patients who received QINLOCK *[see Adverse Reactions (6.1)]*. 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 Dosage and Administration (2.2)]*.

5.2 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 patients, respectively.

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

5.3 Hypertension

In INVICTUS, Grade 1-3 hypertension occurred in 14% of the 85 patients who received QINLOCK, including Grade 3 hypertension in 7% *[see Adverse Reactions (6.1)]*.

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 Dosage and Administration (2.2)]*.

5.4 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 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 Dosage and Administration (2.2)]*.

5.5 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.

5.6 Photosensitivity

QINLOCK may cause photosensitivity reactions. In all patients treated with QINLOCK in clinical trials (n=621), photosensitivity reactions occurred in 0.6% of patients.

Advise patients to limit direct ultraviolet exposure during treatment with QINLOCK and for at least one week after discontinuation of treatment.

5.7 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, QINLOCK can cause fetal harm when administered to a pregnant woman. Oral administration of ripretinib to pregnant rats and rabbits during the period of organogenesis resulted in malformations primarily associated with the cardiovascular and skeletal systems, anatomic variations, decreased fetal body weight, and increased post-implantation loss at exposures approximately one half of the recommended dose of 150 mg once daily based on area under the curve (AUC).

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with QINLOCK and for at least 1 week after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with QINLOCK and for at least 1 week after the last dose *[see Use in Specific Populations (8.1, 8.3), Nonclinical Toxicology (13.1)]*.

A barrier method contraception should be added if systemic contraceptive steroids are used.

5.8 Effects on ability to drive and use machines

QINLOCK has no influence on the ability to drive and use machines. In some patients, fatigue has been reported following administration of QINLOCK. If a patient experiences fatigue, this may influence their ability to drive or use machines.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed elsewhere in the labeling:

- Palmar-Plantar Erythrodysesthesia Syndrome *[see Warnings and Precautions (5.1)]*
- New Primary Cutaneous Malignancies *[see Warnings and Precautions (5.2)]*
- Hypertension *[see Warnings and Precautions (5.3)]*
- Cardiac Dysfunction *[see Warnings and Precautions (5.4)]*
- Photosensitivity [*see Warnings and Precautions (5.6)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Unless otherwise specified, the pooled safety population described in the WARNINGS AND PRECAUTIONS reflect exposure to QINLOCK as a single agent in 351 patients with advanced solid tumors enrolled in either an open-label dose finding with cohort expansion trial or INVICTUS. Among the patients who received QINLOCK in these trials, 52% were exposed for 6 months or longer and 21% were exposed for greater than one year.

Gastrointestinal Stromal Tumor

Patients Who Received Prior Treatment with Imatinib, Sunitinib and Regorafenib

The safety of QINLOCK was evaluated in INVICTUS *[see Clinical Studies (14)]*. Patients received QINLOCK 150 mg taken orally once daily (n=85) or placebo (n=43). Among the patients who received QINLOCK, 46% were exposed for 6 months or longer and 3.5% were exposed for greater than one year.

Serious adverse reactions occurred in 31% of patients who received QINLOCK. Serious adverse reactions that occurred in >2% of patients were abdominal pain (4.7%), anemia (3.5%), nausea (2.4%), and vomiting (2.4%).

Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received QINLOCK. Adverse reactions resulting in permanent discontinuation in ≥1% of patients included general physical health deterioration (2.4%), anemia (1.2%), cardiac failure (1.2%), PPES (1.2%), and vomiting (1.2%).

Dosage interruptions due to an adverse reaction occurred in 24% of patients who received QINLOCK. Adverse reactions requiring dosage interruption in >2% of patients included nausea (3.5%), increased blood bilirubin (2.4%), and PPES (2.4%).

Dose reductions due to an adverse reaction occurred in 7% of patients who received QINLOCK. Adverse reactions resulting in a dose reduction in ≥1.2% of patients were abdominal pain, agitation, alopecia, arthritis, dermatosis, gastrointestinal disorder, hyperesthesia, myalgia, PPES, and decreased weight.

The most common adverse reactions (≥20%), were alopecia, fatigue, nausea, abdominal pain, constipation, myalgia, diarrhea, decreased appetite, PPES, and vomiting. The most common Grade 3 or 4 laboratory abnormalities (≥4%) were increased lipase and decreased phosphate.

Table 2 summarizes the adverse reactions in INVICTUS.

Table 2: Adverse Reactions (≥10%) in Patients with Gastrointestinal Stromal Tumor Who Received QINLOCK in INVICTUS

Adverse Reaction	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 erythrodysesthesia 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 edema	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
Diarrhea	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				
Dyspnea	13	0	0	0

Table 3 summarizes the laboratory abnormalities in INVICTUS.

Table 3: Select Laboratory Abnormalities (≥10%) Worsening from Baseline in Patients with Gastrointestinal Stromal Tumor Who Received QINLOCK with a Difference Between Arms of >5% Compared to Placebo in INVICTUS

Laboratory Abnormality	**QINLOCK[a] (N=85)**		**Placebo[a] (N=43)**	
	Grades 1-4	**Grades 3-4[b]**	**Grades 1-4**	**Grades 3-4**
Hematology				
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 normalized ratio; AST=aspartate aminotransferase; 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.

Other Adverse Reactions

Clinically relevant adverse reactions that occurred in <10% of patients in the pooled safety population included cardiac ischemic events (1.1%) (including acute coronary syndrome and fatal cardiac arrest or myocardial infarction). Photosensitivity occurred in 0.6% *[see Warnings and Precautions (5.6)]*.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on QINLOCK

Table 4 includes drug interactions that affect the pharmacokinetics of ripretinib.

Table 4: Drug Interactions that Affect QINLOCK

Strong CYP3A Inhibitors	
Clinical Impact	• Coadministration of QINLOCK with a strong CYP3A inhibitor increased the exposure of ripretinib and its active metabolite (DP-5439), which may increase the risk of adverse reactions *[see Clinical Pharmacology (12.3)]*.
Prevention or Management	• Monitor patients more frequently for adverse reactions.
Strong and Moderate CYP3A Inducers	
Clinical Impact	• Coadministration of QINLOCK with a strong CYP3A inducer decreased the exposure of ripretinib and its active metabolite (DP-5439), which may decrease QINLOCK anti-tumor activity *[see Clinical Pharmacology (12.3)]*. • Coadministration of QINLOCK with moderate CYP3A inducers is predicted to decrease the exposure of ripretinib and its active metabolite (DP-5439), which may decrease QINLOCK anti-tumor activity *[see Clinical Pharmacology (12.3)]*.
Prevention or Management	• Avoid concomitant use of QINLOCK with strong CYP3A inducers. • Avoid concomitant use of QINLOCK with moderate CYP3A inducers. If a moderate CYP3A inducer cannot be avoided, increase 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 *[see Dosage and Administration (2.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action *[see Clinical Pharmacology (12.1)]*, QINLOCK can cause fetal harm when administered to a pregnant woman. There are no available data on the use of QINLOCK in pregnant women to inform a drug-associated risk. Administration of ripretinib to pregnant rats and rabbits during the period of organogenesis resulted in malformations primarily associated with the cardiovascular and skeletal systems, anatomic variations, reduced fetal body weight, and increased

post-implantation loss at maternal exposures that were approximately equal to the human exposure at the recommended dose of 150 mg (see *Data*). Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

In an embryo-fetal development study investigating daily doses of ripretinib administered during the period of organogenesis in rats, ripretinib resulted in malformations primarily associated with the cardiovascular and skeletal systems, including interrupted or retroesophageal aortic arch and retroesophageal subclavian artery, fusion of the exoccipital bone to the first cervical vertebra, branched and fused ribs, anomalies of the cervical, thoracic, caudal, and sacral vertebrae, absent forepaw phalanges, and absent metacarpals at a dose of 20 mg/kg/day (approximately one half of the human exposure at the recommended dose of 150 mg). An increased incidence of anatomic variations were also observed 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.

In a preliminary embryo-fetal development study investigating the administration of ripretinib in rabbits during the period of organogenesis, ripretinib resulted in total loss of pregnancy at doses of 150 mg/kg (approximately 3.5 times the human exposure at the recommended dose of 150 mg). At a dose of 40 mg/kg (approximately 2.1 times the human exposure at the recommended dose of 150 mg), toxicities included increased post-implantation loss and decreased fetal body weights.

8.2 Lactation

Risk Summary

There are no data regarding the presence of ripretinib or its metabolites in either human milk or its effects on a breastfed child or on milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with QINLOCK and for at least 1 week after the last dose.

8.3 Females and Males of Reproductive Potential

QINLOCK can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status of females of reproductive potential prior to the initiation of QINLOCK *[see Use in Specific Populations (8.1)]*.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment and for at least 1 week after the last dose.

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment and for at least 1 week after the last dose.

Infertility

Based on findings from animal studies, QINLOCK may impair fertility in males of reproductive potential *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of QINLOCK in children and adolescents under the age of 18 years have not been established.

Animal Toxicity Data

In 13-week repeat-dose studies in rats there were dose-dependent findings of increased osteoblastic surface and decreased trabeculae of the femur at doses ≥30 mg/kg/day (approximately one half of the human exposure at the recommended dose of 150 mg). There were additional findings of missing or discolored teeth that were accompanied by dose-dependent incisor degeneration at doses ≥30 mg/kg/day.

8.5 Geriatric Use

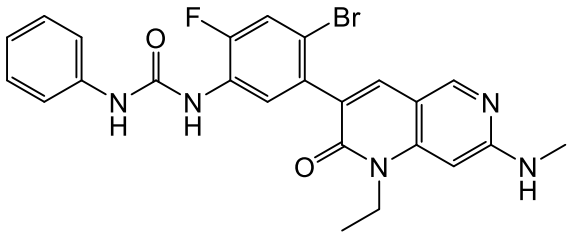
Of the 85 patients in INVICTUS who received QINLOCK 150 mg orally once daily, 24% were between 65 to 74 years of age and 9% were 75 years of age or older. Clinical studies of QINLOCK did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently from younger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

8.6 Hepatic Impairment

No dose adjustment is recommended in patients with mild hepatic impairment (total bilirubin ≤ULN and AST >ULN or total bilirubin 1 to 1.5 × ULN and any AST). A recommended dosage of QINLOCK has not been established for patients with moderate or severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

Ripretinib is a kinase inhibitor. 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. The molecular formula is $C_{24}H_{21}BrFN_5O_2$ and the molecular weight is 510.36 g/mol. The chemical structure of ripretinib is shown below:



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

QINLOCK is available as a white to off-white, oval tablets for oral use containing 50 mg of ripretinib. The tablet is debossed with “DC1” on one side. Each tablet contains the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, hypromellose acetate succinate (HPMCAS-HG), crospovidone, silicon dioxide, and magnesium stearate.

12 CLINICAL PHARMACOLOGY

12.1 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.

12.2 Pharmacodynamics

Exposure-Response Relationships

Ripretinib exposure-response relationships and the time course of pharmacodynamics have not been fully characterized.

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.

12.3 Pharmacokinetics

The pharmacokinetics of ripretinib and its equally active metabolite (DP-5439) were characterized in clinical studies. In patients with advanced malignancies, ripretinib AUC_{0-24h} increased proportionally over a dose range of 20-250 mg (0.13 to 1.67 times the recommended dose), but C_{max} was less than dose proportional; DP-5439 C_{max} and AUC_{0-24h} were less than dose proportional within the dose range of 50-250 mg (0.33 to 1.67 times the recommended dose).

No clinically significant differences in the C_{max} and AUC_{0-24h} were observed between administration of QINLOCK with a high-fat meal (150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively) and under fasted conditions. The pharmacokinetic parameters of ripretinib and DP-5439 are summarized in Table 5.

Table 5: Pharmacokinetic Parameters of Ripretinib and DP-5439

Parameter		Ripretinib	DP-5439
General Information			
Steady state exposure following QINLOCK 150 mg once daily [Mean (CV%)]	C_{max} (ng/mL)	761 (32)	804 (46)
	AUC_{0-12h} (ng•h/mL)	5678 (32)	7138 (44)
Time to steady state [Days]		14	14
Accumulation ratio (AUC_{0-12h}) [Mean (CV%)][a]		1.7 (55)	5.29 (49)
Absorption			
T_{max} [Median in hours][b]		4	15.6
Distribution			
Plasma protein binding (in vitro)	Human serum albumin	99.8%	99.7%
	α-1 acid glycoprotein	99.4%	>99.8%
Steady state apparent volume of distribution, L [Mean (CV%)][b]		307 (39)	507 (51)
Elimination			
Apparent clearance, L/hr [Mean (CV%)][b]		15.3 (45)	17.5 (63)

Half-life, hours [Mean (CV%)][b]		14.8 (30)	17.8 (23)
Metabolism			
Metabolic pathways	Major	CYP3A4	CYP3A4
	Minor	CYP2C8 and CYP2D6	CYP2C8, CYP2E1 and CYP2D6
Excretion			
Excretion pathways	Feces	34%	6%
	Urine	0.02%	0.1%

[a.] Estimated based on cycle 1, day 15

[b.] After a single oral dose of 150 mg

CV=coefficient of variation; C_{max}=maximum plasma concentration; AUC_{0-12h}=area under the plasma concentration-time curve from time zero to 12 hours; AUC_{0-24h}=area under the plasma concentration-time curve from time zero to 24 hours; T_{max}=time to maximum concentration

Specific Populations

No clinically significant 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), tumor (GIST or other solid tumors), prior gastrectomy, mild to moderate renal impairment (CLcr 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 AST any). The effects of severe renal impairment (CLcr 15 to 29 mL/min) or moderate to severe hepatic impairment (total bilirubin >1.5 × ULN, AST any) on the pharmacokinetics of ripretinib have not been studied.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Strong CYP3A Inhibitors: Coadministration of QINLOCK with itraconazole (a strong CYP3A inhibitor and also a P-gp inhibitor) increased ripretinib C_{max} by 36% and AUC_{0-inf} by 99% and also increased DP-5439 AUC_{0-inf} by 99% with no change in its C_{max}.

Strong CYP3A Inducers: Coadministration of QINLOCK with rifampin (a strong CYP3A inducer) decreased ripretinib C_{max} by 18% and AUC_{0-inf} by 61% and also decreased DP-5439 AUC_{0-inf} by 57% with increased C_{max} by 37%.

Moderate CYP3A Inducers: Coadministration of QINLOCK with efavirenz (a moderate CYP3A inducer) was predicted to decrease ripretinib C_{max} by 24% and decrease AUC_{0-inf} by 56%.

Proton Pump Inhibitors: No clinically significant differences in the plasma exposure to ripretinib and DP-5439 were observed when QINLOCK was coadministered with pantoprazole (a proton pump inhibitor).

In Vitro Studies

CYP Enzymes: Ripretinib and DP-5439 are inhibitors of CYP2C8. Ripretinib and DP-5439 are not inducers of CYP1A2, CYP2B6, or CYP3A4.

Transporter Systems: Ripretinib is an inhibitor of P-gp (P-glycoprotein) and BCRP (Breast Cancer Resistance Protein). DP-5439 is a substrate for P-gp and BCRP. DP-5439 is an inhibitor of BCRP and MATE1 (Multidrug And Toxin Extrusion Protein 1).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with ripretinib.

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

Dedicated fertility studies in male animals were not conducted with ripretinib. Findings in male reproductive organs occurred in repeat-dose toxicity studies and included degeneration of the testes and cellular debris of the epididymis in males administered ≥30 mg/kg/day (approximately one half of the human exposure at the recommended dose of 150 mg).

14 CLINICAL STUDIES

The efficacy of QINLOCK was evaluated in INVICTUS, an international, multi-center, randomized (2:1), double-blind, placebo-controlled trial (NCT03353753). Eligible patients had unresectable, locally advanced or metastatic gastrointestinal stromal tumor (GIST) and had received prior treatment with imatinib, sunitinib, and regorafenib. Randomization was stratified by prior lines of therapy (3 versus ≥4) and Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1 or 2). Patients received QINLOCK 150 mg or placebo orally once daily until disease progression or unacceptable toxicity. Tumor 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 tumor nodule within a pre-existing tumor 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 randomized to receive placebo could be treated with QINLOCK at the time of disease progression.

A total of 129 patients were randomized, 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 randomized to placebo switched to QINLOCK after disease progression.

Efficacy results from INVICTUS are summarized in Table 6.

Table 6: Efficacy Results of INVICTUS

	QINLOCK (N=85)	**Placebo (N=44)**
Progression-Free Survival[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)[c]	0.15 (0.09, 0.25)	
p-value[b]	< 0.0001	
Overall Response Rate[a]		
Overall Response Rate (%)	9	0
(95% CI)	(4.2, 18)	(0, 8)
p-value[d]	0.0504	
Overall Survival [e]		
Number of deaths (%)	26 (31)	26 (59)
Median OS (months) (95% CI)	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. p-value is based on 2-sided stratified log-rank test.

c. Hazard ratio is based on Cox proportional regression model. This model includes treatment and randomization stratification factors as fixed factors.

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

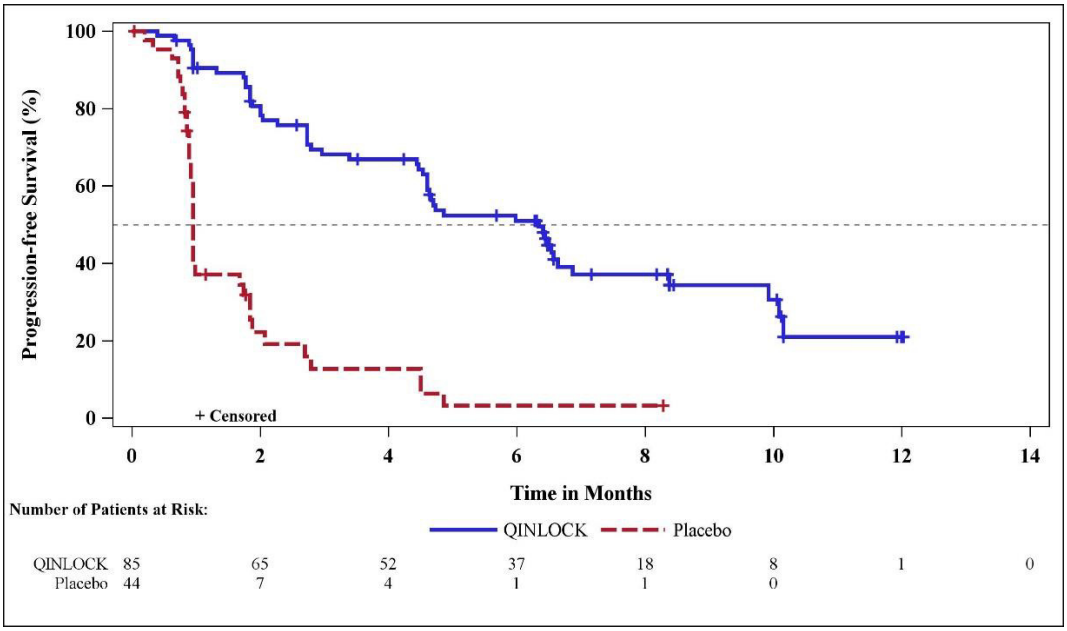
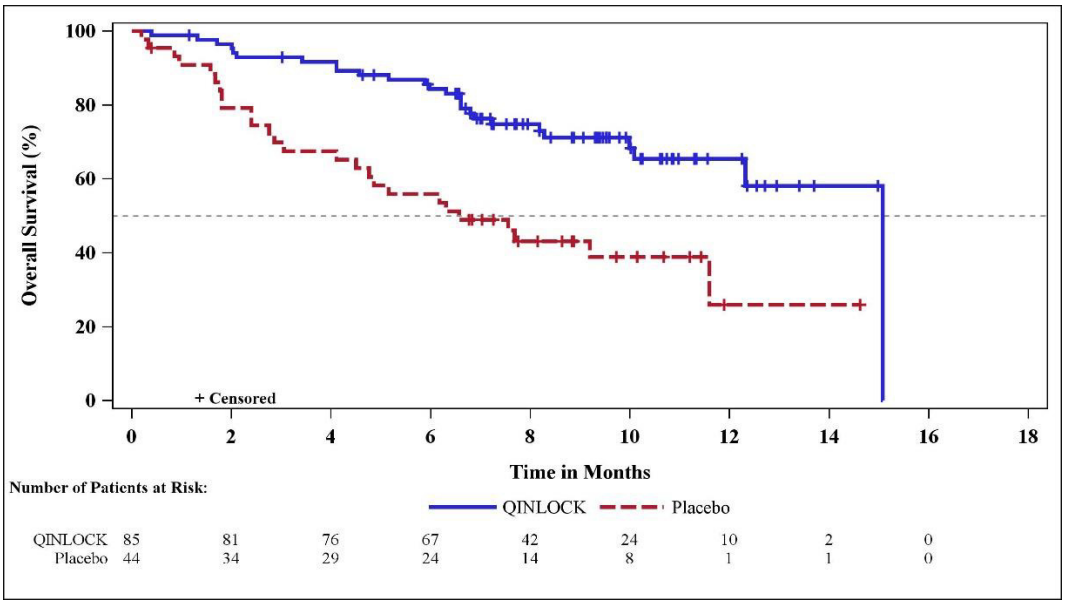


Figure 2: Kaplan-Meier Curve of Overall Survival in INVICTUS



16 HOW SUPPLIED/STORAGE AND HANDLING

QINLOCK 50 mg tablets are white to off-white, oval shaped, and debossed with “DC1” on one side. 90-count bottles.

Store in the original container with the desiccant to protect from moisture and light. Replace cap securely each time after opening. Do not discard desiccant.

Store below 25°C.

17 MANUFACTURER

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18 LICENSE HOLDER

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19 REGISTRATION NUMBER: 171-40-36884-99

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