QINLOCK™
(ripretinib) 50 mg tablets

Dual Locks, Broad Spectrum. Reliable Protection

NCCN PREFERRED CATEGORY 1

QINLOCK® is **recommended** for 4th-line advanced GIST by the National Comprehensive Cancer Network® (NCCN®)[1]

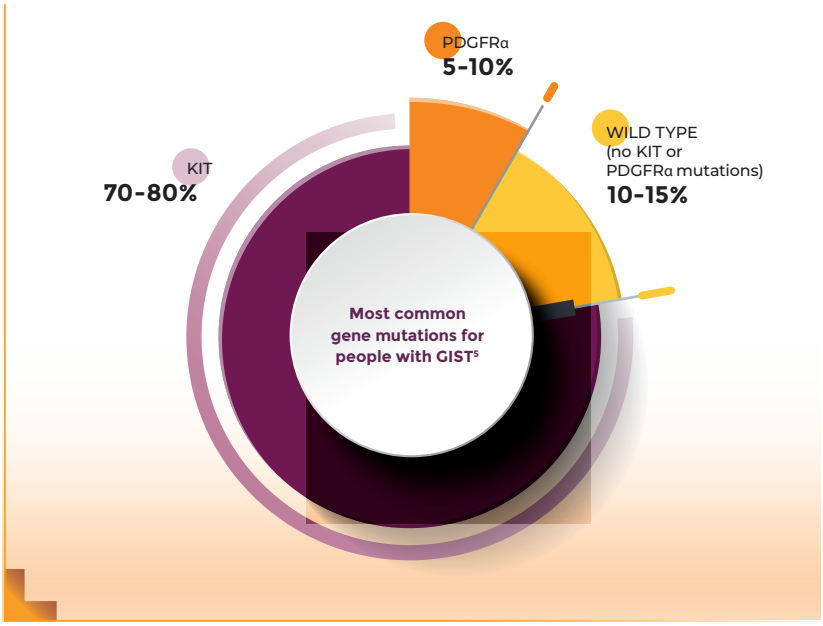
Indication:

Qinlock is a kinase inhibitor indicated for the treatment of adult patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with imatinib, sunitinib, and regorafenib[2]

Strive to identify and address the unmet need of patients with advanced GIST

What is GIST?

- A rare cancer that affects the GI tract, often in the stomach or small intestine.[3] The cause of GIST is unknown; no known lifestyle factors that cause GIST.[4]

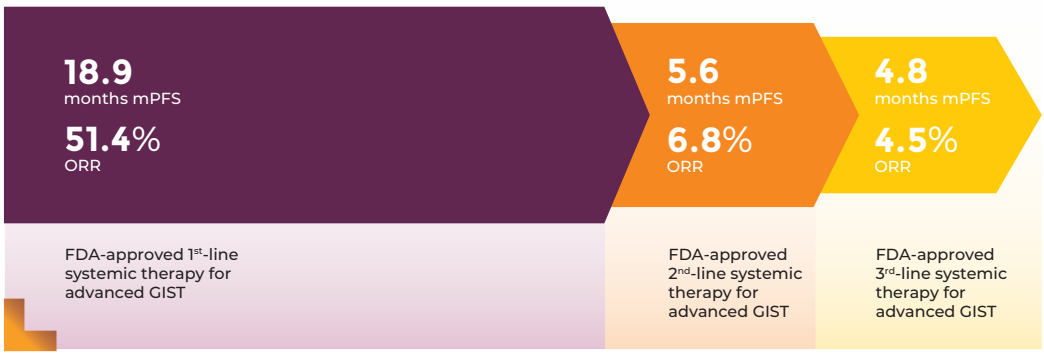


Advanced GIST*[5-7]

- Activating mutations in several domains within KIT and PDGFRα lead to dysregulated kinase receptor signaling[7]
- Secondary resistance often develops due to secondary KIT or PDGFRα mutations[5]
- Also implying tumor resistance to current targeted therapy, or disease progression[5]

As drug resistance develops, treatments may lose their ability to control disease progression[5]

Patients with recurrent GIST tend to progress faster through 2nd- and 3rd-line therapies[8-11]



In the past, there were no approved therapies for 4th-line advanced GIST

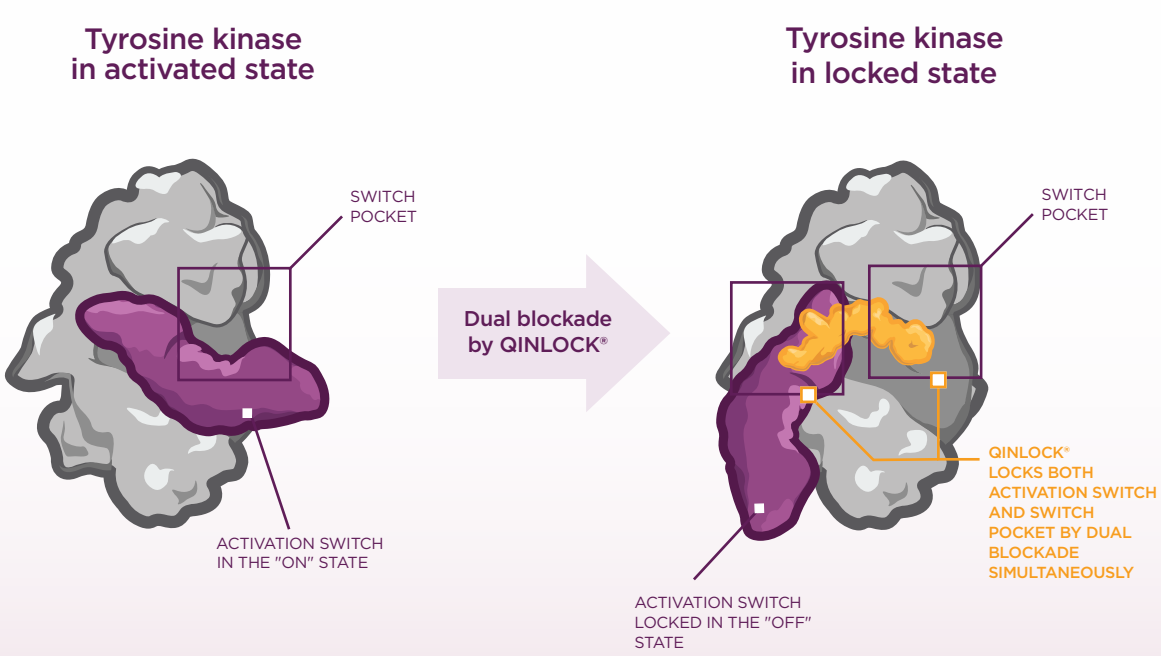
*Advanced GIST includes locally advanced and metastatic GIST[6]

Abbreviations: FDA: Food and Drug Administration; GI: Gastrointestinal; GIST: Gastrointestinal stromal tumors; KIT: Proto-oncogene encoding receptor tyrosine kinase protein; mPFS: Median progression-free survival; ORR: Objective response rate; PDGFRα: Platelet-derived growth factor receptor alpha

The broad spectrum TKI for advanced GIST

What is QINLOCK®?

QINLOCK® is a switch-control TKI with dual blockade and is designed to specifically **inhibit mutant KIT and PDGFRα kinases.**[12]

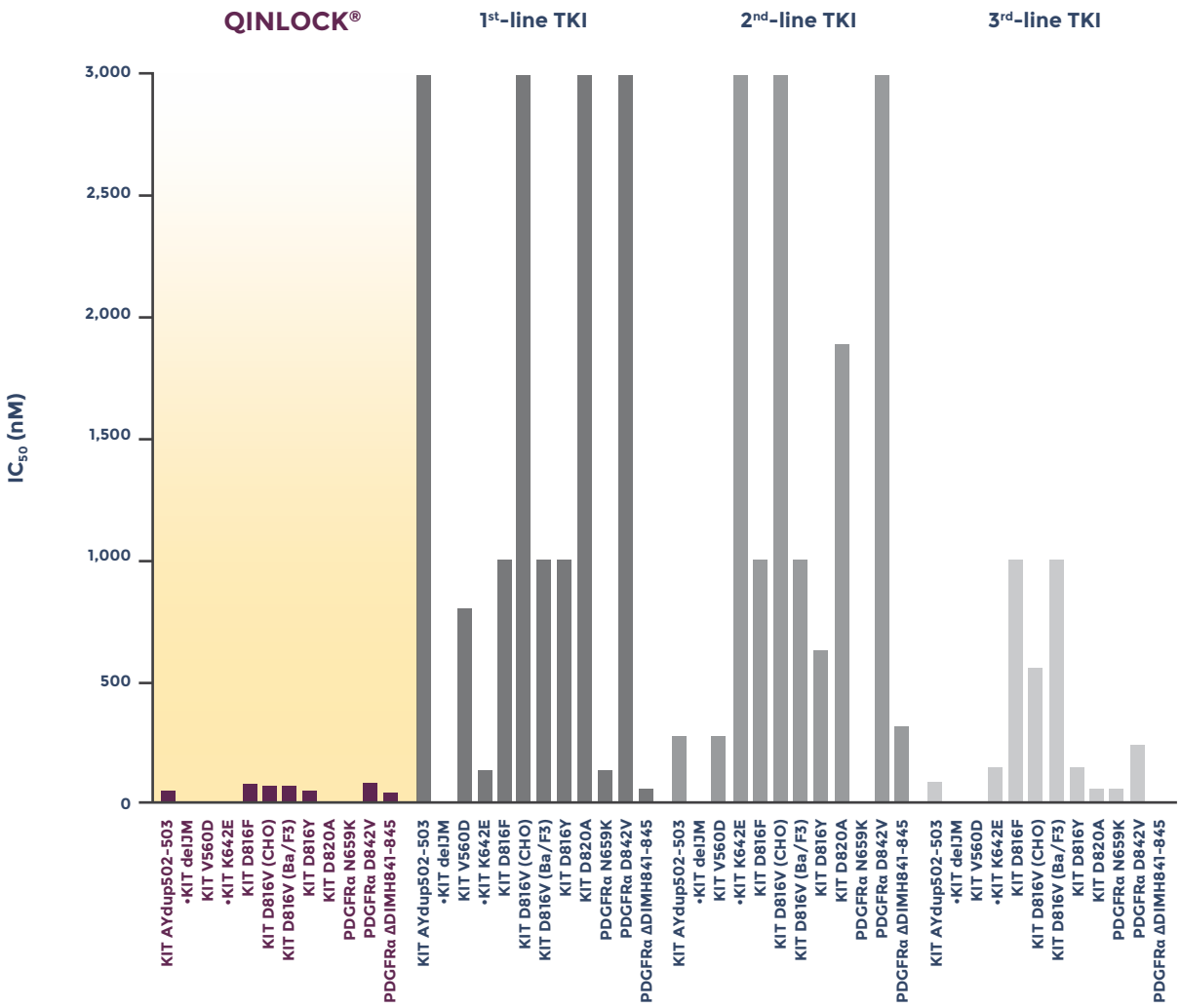


QINLOCK® has been shown to inhibit a **broad spectrum** of KIT/PDGFRα mutations in advanced GIST patients who have received ≥3 prior lines of TKIs including imatinib[12]

Abbreviations: GIST: Gastrointestinal stromal tumor; KIT: Proto-oncogene encoding receptor tyrosine kinase protein; PDGFRα: Platelet-derived growth factor receptor alpha; TKI: Tyrosine kinase inhibitor

The broad inhibitory activity of QINLOCK® against KIT and PDGFRα mutants[13]

The broad inhibitory activity of QINLOCK® against a range of KIT and PDGFRα mutations was demonstrated in preclinical studies*[13]



The low IC_{50} of QINLOCK® across different KIT and PDGFRα mutations indicates the broad coverage and high sensitivity of QINLOCK®[13]

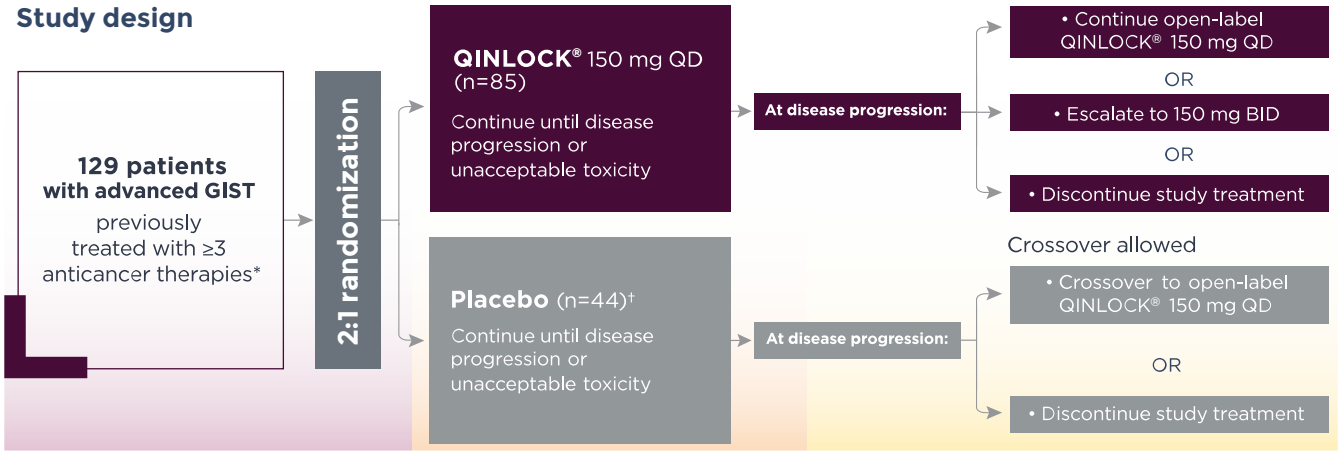
*In vitro studies are not designed to assess clinical efficacy.[13]

Abbreviations: IC_{50}: Half (50%) maximal inhibitory concentration; KIT: Proto-oncogene encoding receptor tyrosine kinase protein; PDGFRα: Platelet-derived growth factor receptor alpha; TKI: Tyrosine kinase inhibitor

Overcome resistances and provide substantial PFS benefits

The INVICTUS study was a global, multicenter, randomized, double-blind, placebo-controlled Phase 3 trial in 129 patients who had received ≥3 prior anticancer therapies for advanced GIST[6]

Study design



Primary endpoint:[6]

- Progression-free survival, based on BICR using modified RECIST 1.1 criteria‡

Key secondary endpoint:[6]

- Objective response rate based on BICR

Additional secondary endpoints:[6]

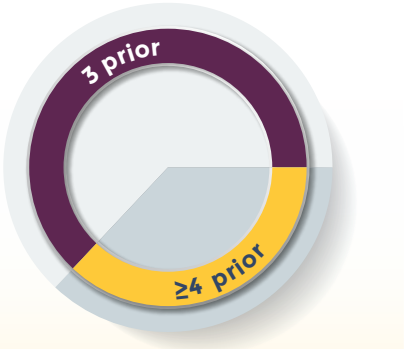
- Overall survival
- Quality of life
- Safety

*Patients were stratified according to prior treatments (3 vs ≥4) and ECOG PS (0 vs 1 or 2).[6]
†44 patients were randomized to placebo, but one did not receive treatment.[6]
‡Lymph nodes and bone lesions were not target lesions and progressively growing new tumor nodule within pre-existing tumor mass was progression as defined in protocol.[6]

A wide range of advanced GIST patients were enrolled in INVICTUS[6,14]

Majority of patients in INVICTUS were heavily pre-treated.[6,14]

64% of patients had received 3 prior therapies[6]



36% of patients had received ≥4 prior therapies[6]

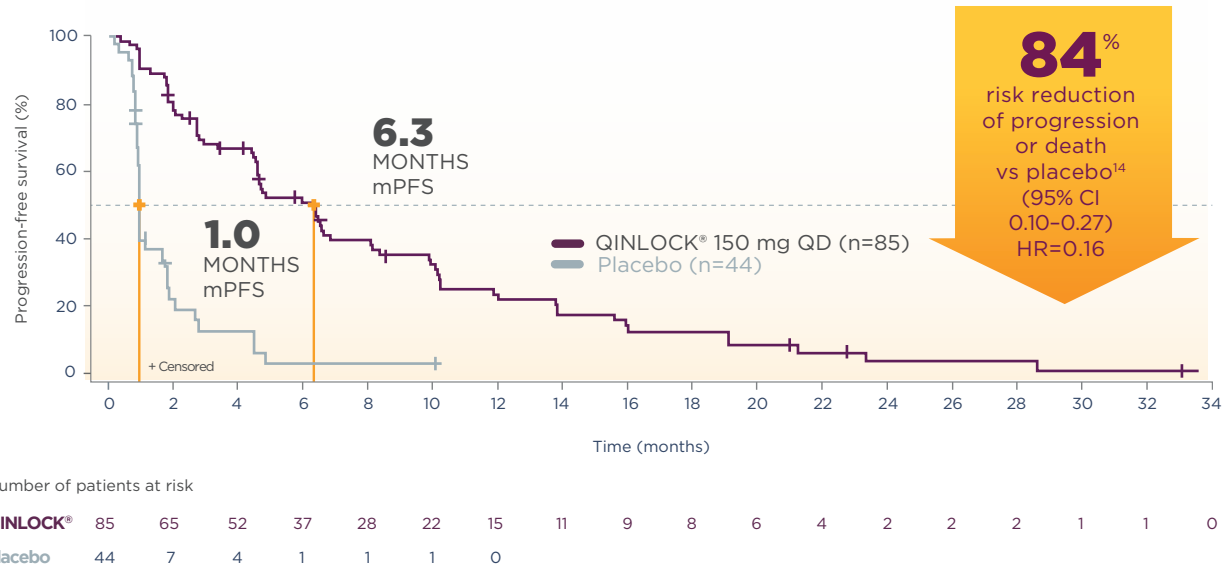
Selected baseline characteristics[14]	QINLOCK® (n=85)	Placebo (n=44)
Age, median (range), years	59 (29-82%)	65 (33-83%)
18-64	57 (67%)	22 (50%)
65-74	20 (24%)	12 (27%)
≥75	8 (9%)	10 (23%)
Sex		
Male	47 (55%)	26 (59%)
Female	38 (45%)	18 (41%)
ECOG PS		
0	37 (44%)	17 (39%)
1/2	48 (56%)	27 (61%)
Number of prior therapies		
3	54 (64%)	27 (61%)
≥4§ (range, 4-7)	31 (36%)	17 (39%)
Primary mutation (central testing of tumor tissue)		
KIT exon 9	14 (17%)	6 (14%)
KIT exon 11	47 (55%)	28 (64%)
Other KIT	2 (2%)	2 (5%)
PDGFRα	3 (4%)	0
KIT/PDGFRα wild type	7 (8%)	3 (7%)
Not available/not done‖	12 (14%)	5 (11%)

Data are presented as n (%) unless otherwise noted.
§In addition to imatinib, sunitinib, and regorafenib, prior therapies received by ≥5% patients included pazopanib, nilotinib, sorafenib, and avapritinib.[14]
‖Not available=tumor tissue analyzed for baseline mutations but analysis failed; Not done=biopsy completed per protocol but sample not received for analysis.[14]

Abbreviations: BICR: Blinded independent central review; BID: Twice a day; ECOG: Eastern Cooperative Oncology Group; GIST: Gastrointestinal stromal tumor; KIT: Proto-oncogene encoding receptor tyrosine kinase protein; PDGFRα: Platelet-derived growth factor receptor alpha; PFS: Progression-free survival; PS: Performance status; QD: Once daily; RECIST: Response Evaluation Criteria in Solid Tumours

QINLOCK® demonstrated powerful PFS results

QINLOCK® prolonged PFS by 5.3 months: 6.3 months vs 1.0 month with placebo with a 36 months follow-up[14]



Number of patients at risk

QINLOCK®	85	65	52	37	28	22	15	11	9	8	6	4	2	2	2	1	1	0
Placebo	44	7	4	1	1	1	0											

Estimated landmark PFS	QINLOCK® (n=85)	Placebo (n=44)
6-months PFS (95% CI)	**51.0%** (39.4–61.4)	**3.2%** (0.2–13.8)
12-months PFS (95% CI)	**22.2%** (13.4-32.4)	**NE** (NE–NE)
18-months PFS (95% CI)	**11.8%** (5.6-20.6)	**NE** (NE–NE)

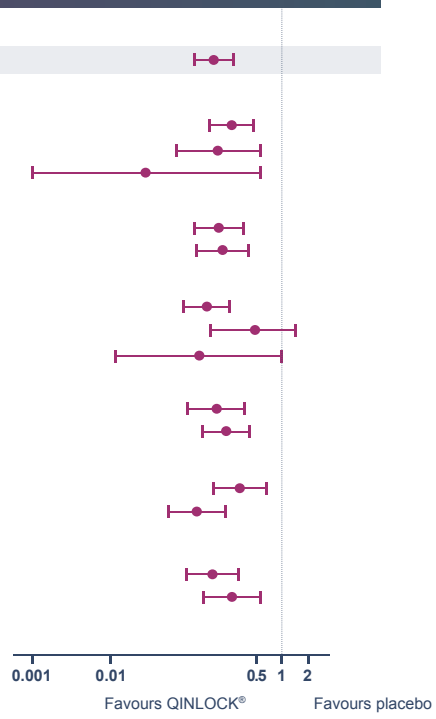
Abbreviations: CI: Confidence interval; HR: Hazard ratio; mPFS: Median progression-free survival; NE: Not estimable; PFS: Progression-free survival; QD: Once daily

Consistent PFS benefits of QINLOCK® among different subgroups[12,14]

QINLOCK® provided generally consistent PFS results across different patient and mutation subgroups[12,14]

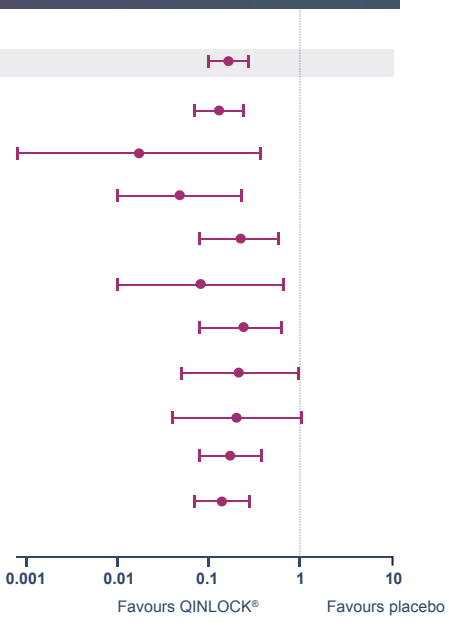
PFS results of QINLOCK® across different patient subgroups after a median follow-up of 36 months[14]

Subgroup	QINLOCK® 150 mg QD (n)	Placebo (n)	Hazard ratio (95% CI)
INVICTUS ITT population	85	44	**0.16** (0.10, 0.27)
Age group			
18-64 years	57	22	**0.26** (0.14, 0.46)
65-74 years	20	12	**0.18** (0.06, 0.56)
≥75	8	10	**0.03** (0.00, 0.56)
Sex			
Male	47	26	**0.18** (0.10, 0.35)
Female	38	18	**0.20** (0.10, 0.39)
Race			
White	64	33	**0.14** (0.07, 0.25)
Non-white	13	7	**0.46** (0.15, 1.42)
Not reported	8	4	**0.11** (0.01, 0.97)
Country			
US	40	20	**0.17** (0.08, 0.34)
Non-US	45	24	**0.23** (0.12, 0.43)
Screening ECOG			
0	38	19	**0.34** (0.16, 0.69)
1 or 2	47	25	**0.10** (0.05, 0.21)
Prior systemic anticancer treatments			
3	54	27	**0.15** (0.08, 0.29)
≥4	31	17	**0.27** (0.13, 0.55)



PFS results of QINLOCK® across different mutation subgroups[12]

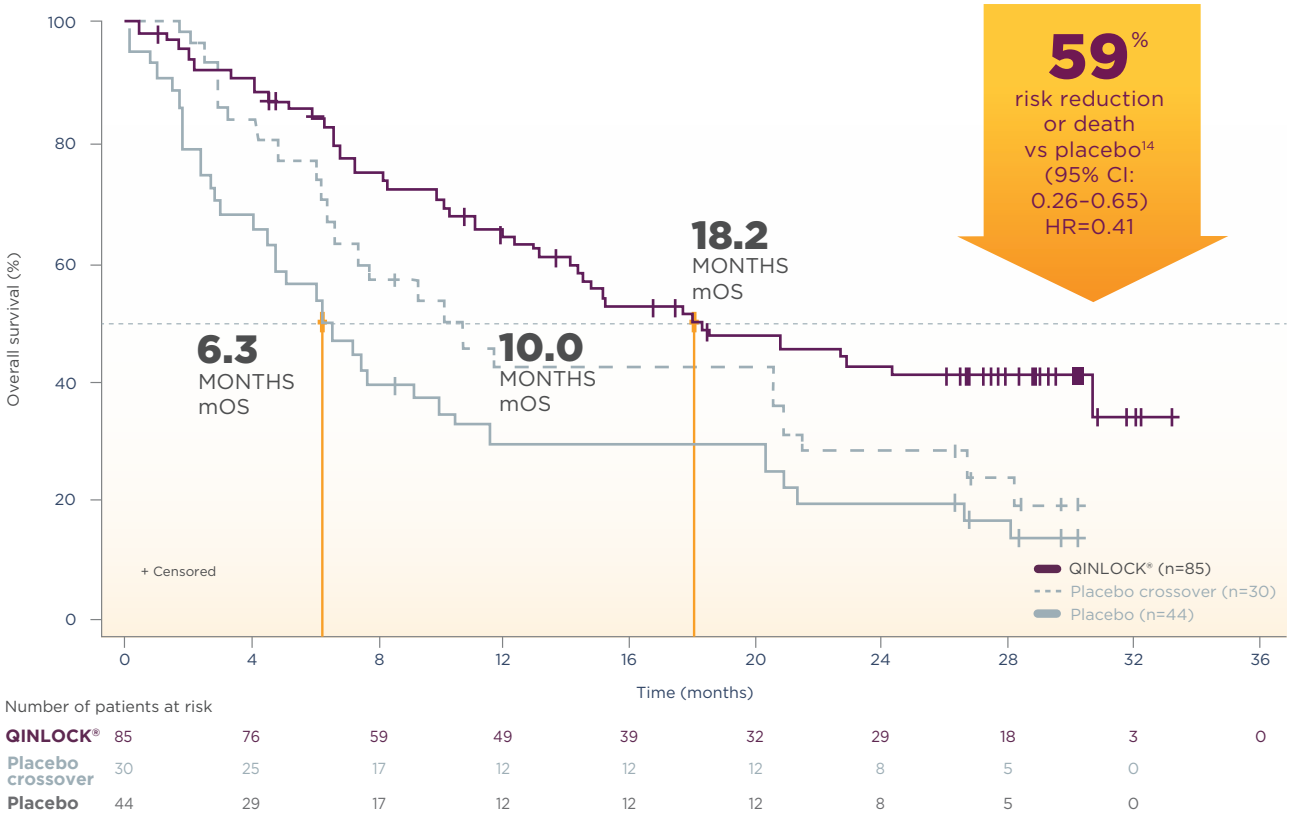
Mutation subgroup	QINLOCK® 50 mg QD (n)	Placebo (n)	Hazard ratio (95% CI)
INVICTUS ITT population	85	44	**0.16** (0.10, 0.27)
Any KIT exon 11	52	34	**0.13** (0.07, 0.24)
Exon 11 + 13 only	8	5	**0.04** (0.00, 0.37)
Exon 11 + 17	20	14	**0.05** (0.01, 0.23)
Exon 11 + 13 + 17	16	9	**0.22** (0.08, 0.58)
Other	8	6	**0.07** (0.01, 0.66)
Any KIT exon 9	16	7	**0.22** (0.08, 0.63)
Exon 9 + 17	7	4	**0.21** (0.05, 0.95)
Exon 9 only	9	3	**0.20** (0.04, 1.03)
Any KIT exon 13	27	16	**0.17** (0.08, 0.38)
Any KIT exon 17	44	27	**0.14** (0.07, 0.28)



Abbreviations: CI: Confidence interval; ECOG: Eastern Cooperative Oncology Group; ITT: Intent-to-treat; KIT: Proto-oncogene encoding receptor tyrosine kinase protein; PFS: Progression-free survival; QD: Once daily; US: United States

QINLOCK® prolonged survival of advanced GIST patients[14]

QINLOCK® achieved a median OS of 18.2 months with 36 months of follow-up*[14]



Number of patients at risk

QINLOCK®	85	76	59	49	39	32	29	18	3	0
Placebo crossover	30	25	17	12	12	12	8	5	0	
Placebo	44	29	17	12	12	12	8	5	0	

*OS data includes all time periods, including dose escalation to 150mg BID. Placebo curve includes patients who crossed over to QINLOCK® treatment.[14]

Clinically meaningful improvement in ORR by BICR[14]

11.8% QINLOCK vs. 0.0% Placebo[14]

Median DOR was 14.5 months with QINLOCK® vs. NE with placebo[14]

Abbreviations: BICR: Blinded independent central review; BID: Twice a day; CI: Confidence interval; DOR: Duration of response; GIST: Gastrointestinal stromal tumor; HR: Hazard ratio; mOS: Median overall survival; NE: Not estimable; ORR: Objective response rate; OS: Overall survival

Favorable safety profile of QINLOCK® across a broad range of patients[14]

Safety updates of QINLOCK®[14]

With 36 months of follow-up, safety findings were consistent with the primary analysis results:[14]

- Most TEAEs were Grade 1/2 only
- Alopecia (52%), fatigue (47%), and nausea (41%) remained the most common Grade 1/2 TEAEs
- Grade 3/4 TEAEs were minimal, and there was no Grade 3/4 palmar-plantar erythrodysesthesia

	QINLOCK®		Placebo	
Preferred term, n(%)	**Any grade (n=85)**	**Grade 3/4 (n=85)**	**Any grade (n=43)†**	**Grade 3/4 (n=43)†**
TEAE*				
Alopecia	44 (52%)	N/A	2 (5%)	N/A
Fatigue	40 (47%)	3 (4%)	10 (23%)	1 (2%)
Nausea	35 (41%)	3 (4%)	5 (12%)	0
Abdominal pain	34 (40%)	6 (7%)	13 (30%)	2 (5%)
Constipation	32 (38%)	1 (1%)	9 (21%)	0
Myalgia	31 (37%)	1 (1%)	5 (12%)	1 (2%)
Diarrhoea	28 (33%)	1 (1%)	6 (14%)	1 (2%)
Decreased appetite	25 (29%)	1 (1%)	9 (21%)	2 (5%)
Palmar-plantar erythrodysesthesia	19 (22%)	0	0	0
Vomiting	19 (22%)	3 (4%)	3 (7%)	0

*Top 10 most common TEAEs in patients receiving QINLOCK®[14]
†44 patients were randomized to placebo, but 1 did not receive treatment.[14]

Comparable and minimal AE-related dose modification

TEAEs leading to dose modification or death were comparable to placebo[14]

Parameters, n(%)	QINLOCK®(n=85)	Placebo(n=43)†
Dose interruption	**24 (28%)**	10 (23%)
Dose reduction	**8 (9%)**	1 (2%)
Treatment discontinuation	**7 (8%)**	5 (12%)
Treatment-related death‡	**6 (7%)**	10 (23%)

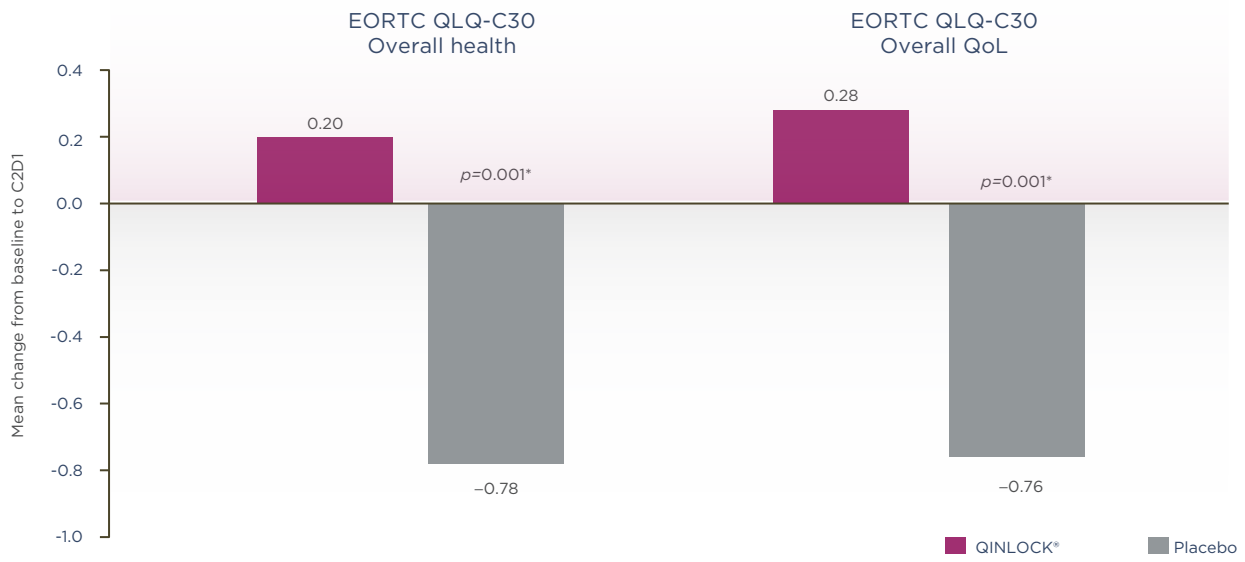
†44 patients were randomized to placebo, but 1 did not receive treatment.[14]
‡3 deaths considered possibly related to blinded study drug; 2 in QINLOCK® arm (respiratory failure and death) and 1 in placebo arm (due to 2 events of septic shock and pulmonary oedema).[14]

Abbreviations: AE: Adverse event; N/A: Not applicable; TEAEs: Treatment-emergent adverse events

QINLOCK® improved QoL and overall health of advanced GIST patients[15]

QINLOCK® enhanced self-reported health status, physical and role functioning of patients[15]

QINLOCK® improved the overall health and overall QoL of patients[15]



*P-values are nominal and no statistical significance is being claimed. The Physical and Role Function questions were rolled up to a score out of 100; questions C29 and C30 are based on 7-point scales.[15]

The improvements in patient-reported outcomes with QINLOCK® were clinically significant ($p \leq 0.004$)[15]

QINLOCK® maintained the overall health and overall QoL of patients treated with QINLOCK® from baseline to cycle 10[15]

Abbreviations: C2D1: Cycle 2 day 1; EORTC QLQ-C30: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L: EuroQol-5D; GIST: Gastrointestinal stromal tumor; QoL: Quality of life; VAS: Visual analogue scale

QD dosing of QINLOCK® and additional clinical benefit with BID dosing upon progression[2,16]

Once-daily dosing

The recommended dose of QINLOCK® is 150mg[2]

(3 x 50mg tablets)

Dosed once daily | **No known dietary restrictions**

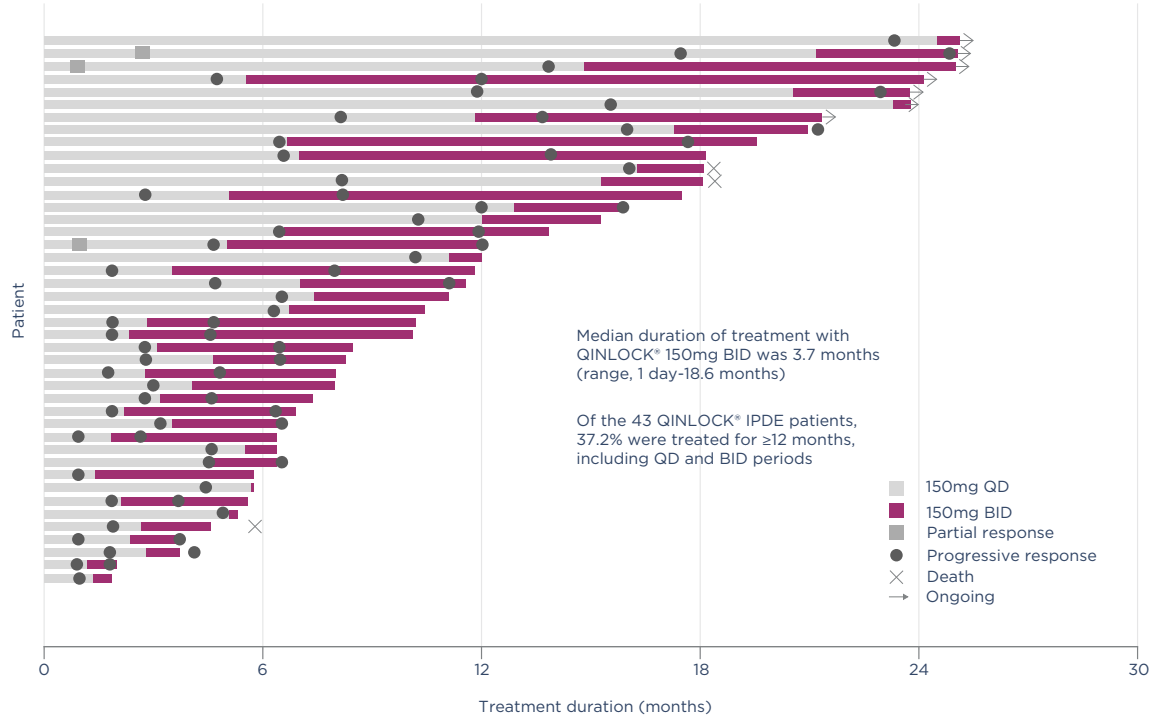
QINLOCK® should be taken at the same time each day[2]

- Advise patients to take all 3 tablets in one sitting, and to swallow tablets whole
- In the event of a missed dose, advise patients to take a replacement dose only if it is within 8 hours of the missed dose
- If the patient vomits after taking a dose, advise him or her not take an additional dose until the next scheduled dose

PFS2 benefits with BID dosing upon progression[16]

NCCN GUIDELINES

An additional clinical benefit may be obtained with the use of QINLOCK® 150mg BID upon progression on QINLOCK® 150mg daily[1]



Patients (n=43) achieved a mPFS1 of 4.6 months with QINLOCK® 150mg QD and obtained a mPFS2 of 3.7 months upon dose escalation to 150mg BID[16]

Abbreviations: BID: Twice a day; GIST: Gastrointestinal stromal tumor; IPDE: Intra-patient dose escalation; mPFS1/2: Median time to first/second objective disease progression; NCCN: National Comprehensive Cancer Network; PFS: Progression-free survival; QD: Once daily

Dual Locks, Broad Spectrum. Reliable Protection

- **Median PFS and the risk of progression or death** were **improved** with QINLOCK® compared with placebo in the Phase III clinical trial[14]
- **Median OS with QINLOCK®** was 18.2 months vs 6.3 months in the placebo arm and vs. 10.0 months in placebo patients crossing over to QINLOCK® with a 36-month follow-up[14]
- **A favorable safety profile** was observed in patients treated with QINLOCK® in the Phase III trial[14]

Abbreviations: OS: Overall survival; PFS: Progression-free survival

References:
1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Gastrointestinal Stromal Tumors (GISTs). **2.** QINLOCK® Full Prescribing Information. Nov 2020. **3.** Mantese, G. Gastrointestinal stromal tumor: epidemiology, diagnosis, and treatment. Curr Opin Gastroenterol. November 2019;35(6):555-559. **4.** https://www.cancer.net/cancer-types/gastrointestinal-stromal-tumor-gist/risk-factors. Accessed on 22 Jun 2022. **5.** Lopes LF, Bacchi CE. Imatinib treatment for gastrointestinal stromal tumor (GIST). *J Cell Mol Med*. 2010;14(1-2):42-50. **6.** Jean YB, et al. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2020. **7.** Hemming ML, et al. Translational insights into gastrointestinal stromal tumor and current clinical advances. Ann Oncol. 2018;29(10):2037-2045. **8.** Demetri GD, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitib: aninternational, multicentre, prospective, randomised, placebo-controlled phase 3 trial (GRID). *Lancet*. 2013;381(9863):295-302. **9.** Gleevec [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2018. **10.** Sutent [package insert]. New York, NY: Pfizer Inc; 2019. **11.** Stivarga [package insert]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc; 2020. **12.** Schöffski P, et al. Ripretinib demonstrated activity across all KIT/PDGFRA mutations in patients with fourth-line advanced gastrointestinal stromal tumor: Analysis from the phase 3 INVICTUS study. Poster presentation at: 2020 Connective Tissue Oncology Society Virtual Meeting; November 18-21 2020. **13.** Smith BD, et al. Ripretinib (DCC-2618) is a switch control kinase inhibitor of a broad spectrum of oncogenic and drug-resistant KIT and PDGFRA variants. *Cancer Cell*. 2019;35(5):738-751. **14.** Mehren MV, et al. Ripretinib as 4th-line treatment in patients with advanced gastrointestinal stromal tumor (GIST) long-term update from the phase 3 INVICTUS study. ESMO Congress Virtual Meeting. September 16-21, 2021. Poster 1540P. **15.** Heinrich MC, et al. Quality of life (QoL) and self-reported function with ripretinib in 4th-line therapy for patients with gastrointestinal stromal tumors (GIST): Analyses from INVICTUS. Poster presented at the 2020 ASCO Annual Virtual Meeting; May 29-31, 2020. **16.** Zalcberg JR, et al. Intra-patient dose escalation (IPDE) of ripretinib after disease progression in patients with advanced gastrointestinal stromal tumor (GIST): Analyses from the phase 3 INVICTUS study. *J Clin Oncol*. 2021,39(suppl 15; abstr 11536).

Abbreviated Prescribing Information

INDICATIONS
Qinlock is indicated for the treatment of adult patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with imatinib, sunitinib, and regorafenib.

DOSAGE AND ADMINISTRATION
150mg (three 50mg tablets) taken orally once daily. Dosage reduction for adverse reaction is 100mg orally once daily. Permanently discontinue QINLOCK in patients who are unable to tolerate 100 mg orally once daily. Please refer to the full prescribing information for recommended dosage modifications for adverse reactions and missed dose. Qinlock is not indicated in pediatrics (<18 years old). No dose adjustment is required for geriatrics (≥65 years old). 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 end-stage renal disease (CrCl <15mL/min estimated by Cockcroft-Gault or requiring dialysis) or severe renal impairment (CrCl 15 to 29 mL/min) have not been studied. 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). The pharmacokinetics and safety of Qinlock in patients with moderate or severe hepatic impairment have not been studied.

CONTRAINDICATIONS
Hypersensitivity to ripretinib or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. WARNINGS AND PRECAUTIONS The following are clinically significant adverse events: 1) Cardiac dysfunction. Cardiac failure and Grade 3 decreased ejection fraction has occurred in clinical study. Cardiac dysfunction has led to dose discontinuation. An assessment of the ejection fraction by echocardiogram or MUGA scan is recommended prior to initiation and during treatment, as clinically indicated. Permanently discontinue Qinlock for Grade 3 or 4 left ventricular systolic dysfunction; 2) Hypertension. Higher incidence of hypertension in patients treated with Qinlock than in placebo-treated patients in clinical study. Do not initiate Qinlock in patients with uncontrolled hypertension. Adequately control blood pressure prior to initiating Qinlock; 3) New primary cutaneous malignancies. Squamous cell carcinoma (SCC) of the skin and melanoma, actinic keratosis, keratoacanthoma and melanoma were reported in patients who received Qinlock in clinical study. Dermatological assessment should be performed when initiating Qinlock and patients should receive dermatological examinations routinely. Other warnings and precautions include cardiac ischaemic events, hypersensitivity, wound healing, reproduction, fertility, palmar-plantar erythrodysesthesia syndrome [PPES] and photosensitivity.

PREGNANCY AND BREAST-FEEDING
Pregnancy - Qinlock should not be administered to pregnant women. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception to commence 2 weeks prior to treatment, during treatment and for at least one complete uterine cycle after the final dose of Qinlock. Breast-feeding - Advise women not to breastfeed during treatment and for at least 2 weeks after the final dose.

ADVERSE REACTIONS
The most common adverse events (≥20%) observed in clinical study were alopecia, fatigue, nausea, abdominal pain, constipation, myalgia, diarrhea, decreased appetite, palmar-plantar erythrodysesthesia syndrome, and vomiting. 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%), anemia (3.5%), nausea (2.4%), vomiting (2.4%). Dosage interruptions due to an adverse event occurred in 23.5% of patients who received Qinlock. Adverse events 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 event occurred in 7.1% of patients who received Qinlock. Adverse events 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. Permanent discontinuation due to an adverse event occurred in 8.2% of patients who received Qinlock. Adverse events 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%).

DRUG INTERACTIONS
In vitro data suggested that CYP3A4/5 is the major metabolizer of ripretinib. Potential interactions may occur with drugs/foods/herbs that are inhibitors or inducers of this enzyme system. Monitor patients more frequently for adverse reactions if Qinlock is given concurrently with a strong CYP3A inhibitor. Avoid concomitant use of Qinlock with strong CYP3A inducers. Monitor patients who ingest grapefruit juiced while taking Qinlock. Avoid concomitant use with St. John's wort. Please refer to the full prescribing information before prescribing.
Ref. HKPI Nov 2020 (Canadian PM 19 Jun 2020)

HK-QIN-202208-01

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QINLOCK™ (ripretinib) 50 mg tablets