Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende ripretinib til behandling af avanceret gastrointestinal stromal tumor

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. ripretinib
2. Forhandlingsnotat fra Amgros vedr. ripretinib
3. Ansøgers endelige ansøgning vedr. ripretinib

29th October 2024

Dear Danish Medicines Council,

Thank you for the opportunity to comment on the draft report for the assessment of ripretinib for the treatment of advanced GIST. We are pleased to see that the clinical value of ripretinib as well as the current unmet medical need of this patient group is recognised. Getting unhindered access to ripretinib would be an advancement for Danish patients and would also enable the treatment as recommended by the ESMO guidelines. Nonetheless, we would like to respond to some of the suggested amendments, namely the off-label use and the changes to the OS data.

Off-label use:

We acknowledge that upon exhaustion of approved treatments, off-label decisions may be made as an exception in clinical practice by the responsible prescribing medical doctor, but *only* on a *specific*, *concrete* and *patient individual* basis. As the Medicines Council will appreciate, any direct or indirect comparison, recommendation or treatment guideline by the Medicines Council that would lead to a general clinical off label BID use of ripretinib, pazopanib and sorafenib is not in line with both Danish and EU law. We understand that cost-effectiveness assessments made versus BSC and in end-of-life context have challenges in capturing the true value of a product. Yet inclusion of off-label salvage treatments as well as off-label ripretinib dosing in the analysis is problematic for the praxis for the ICER. The DMC guidelines are very clear that it is appropriate to compare against placebo under these circumstances of non-evaluated off-label alternatives and it is inherent that the intervention is to be assessed per label. The non-evaluated off-label comparison proposed by the DMC not only contradicts current guidelines but also introduces interpretative difficulties of the resulting ICER.

***Dose escalation**: Ripretinib is *only* approved for the treatment of adult patients with advanced GIST who have received prior treatment with three/more kinase inhibitors with the labelled dosing regimen (150 mg once daily (QD)). This is reflected in the health economic analysis. Hence, *dose escalation* to twice a day (BID) should not be assessed. The BID dose is not included in the label approved by the EC and was *only* permitted upon investigator discretion (on a specific, concrete and individual patient basis) in INVICTUS. This is because the BID dose data from the open label phase of the INVICTUS trial was not deemed to be robust enough to support a claim for this treatment, owing to the lack of a randomised control group and inability to isolate a drug effect. Hence, there are only intra-patient comparisons available from the selected group that received BID upon investigator discretion. These patients progressed the fastest (PFS1 is shorter than in the ITT population) and were deemed able to tolerate an escalated dose. [redacted] Consequently, clinical evolution post PFS event in INVICTUS should not be correlated to Danish clinical practice with dose escalation to BID. Therefore, we strongly reject the contention that dose escalation would be in the realm of 70% of patients.

***Addition of off-label comparator treatments:** The ESMO and Danish treatment guidelines for advanced GIST lift the goal of continuous TKI treatment, with the fewest and shortest possible breaks to avoid the rapid deterioration associated with discontinuation. Up until now, no approved treatment has been available after progression at 3L. In the absence of a SOC treatment, ripretinib was compared with placebo in INVICTUS; the placebo arm mirrors real-world clinical practice with patients receiving BSC and there was an option to cross-over to active treatment upon disease progression. This approach is supported by the EMA and the Declaration of Helsinki and reflects the study design of the clinical trials for the other TKIs approved for the treatment of GIST (imatinib, sunitinib and regorafenib).

Ripretinib is the only recommended treatment at 4L in the guidelines. The use of off-label TKIs outside of clinical studies is explicitly discouraged by ESMO. Hence, we reject the suggestion to include pazopanib (75%) and sorafenib (25%) as salvage treatment in the current analysis. These treatments have not been tested for cost-effectiveness in this disease setting and there is a lack of data on the effectiveness for this

patient group and line of treatment. Under these circumstances, the DMC reimbursement guidelines are very clear that it is appropriate to compare against placebo.

Further, the assumption that all patients would be treated off label is unreasonable. No assumptions have been made that patient have the health status to initiate another treatment after discontinuation of a previous line of treatment. Therefore, this assumption at a later line of treatment would be very inconsistent and not reflect clinical reality. Hence, if such treatments would be included, it is reasonable to assume that only a proportion of patients might initiate off-label salvage treatment.

Changes to the OS data underlying the model:

We strongly reject the suggestion to use the ITT OS data from INVICTUS for BSC in the health economic model. First, the proposed off-label treatments lack robust data in this line of treatment and patient group. On the other hand, the survival benefit for patients in BSC due to cross-over to ripretinib is large, as indicated by an unadjusted ITT median OS for BSC of [redacted] versus [redacted] weeks using cross over adjusted OS. Therefore, using the ripretinib treatment effect as proxy of off-label TKI treatment in fourth line is overly conservative. Second, cross-over adjustment using the two-stage adjustment model with treatment switch and time to progression as co-variates is robust to the inclusion of additional covariates (ECOG PS, age and QoL), both because time to progression was the only statistically significant co-covariate and due to the extended model predicted median OS being [redacted] weeks. Moreover, using TKIs as a last line treatment introduces a disconnect in the current model as the potential impact on survival with TKI treatment is only included in the BSC arm but not as a subsequent treatment in the ripretinib extending OS in the PD-off health state.

Also, as the suggested TKIs have not been previously assessed by the DMC in 4L for the patient group, it is imperative to avoid comparisons with these treatments when evaluating a new pharmaceutical product according to the guidelines. Instead, placebo must be used as the comparator to ensure a robust and fair assessment of the new pharmaceutical's cost-effectiveness.

Regarding BID, we believe that the likely proportion dose escalating in clinical practice would at most be [redacted] after further discussion with the Danish clinical expert and the [redacted] usage we are seeing in launched European markets. Within the range of [redacted] (Deciphera) to 70% (DMC), we propose that [redacted] is as a reasonable compromise in the interest of addressing uncertainty.

We accept the changes proposed by the DMC to the PDOff utility value. For the aforementioned reasons, the revised base case includes the following updates to the submitted base case: 1[redacted] of patients on BID, 2) 0.686 utility value for the PD BSC and PD off health state. The survival analysis is intact. The revised ICER is [redacted] which can be contrasted with the DMC base case ICER of [redacted]. One way of mitigating uncertainty in the present case of two competing ICERs is to use a mid-range estimate of cost-effectiveness, rendering an ICER of [redacted]

Conclusions: As stated above, off-label comparisons, use and general recommendations have the potential to put patient safety at risk. We expect that the Medicines Council will refrain from any such use when finalizing the application process. Further, we sincerely hope that you consider the changes made to the cost-effectiveness assessment in light of the arguments we have presented above. The proposed suggestions align with the clinical reality for 4L patients with advanced GIST and are in line with the health economic guidelines.

Confidentiality: We have noted that the Medicines Council has not made the redactions that we requested in our original submission. As the redactions suggested comprise highly sensitive business information, cf. the Danish Access to Public Files Act, S. 30 (1)(2), we urge the Medicines Council to conduct a reviewed assessment to ensure that the redactions are made as required by the Access to Public Files Act. We expect that the Medicines Council will circulate a new version for our review prior to any publication.

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21.10.2024

CAF/MBA

Forhandlingsnotat

Dato for behandling i Medicinrådet	27.11.2024
Leverandør	Deciphera Pharmaceuticals (Netherlands) B.V.
Lægemiddel	Qinlock (ripretinib)
Ansøgt indikation	Avanceret gastrointestinal stromal tumor, som tidligere er behandlet med tre eller flere kinasehæmmere heriblandt imatinib
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Qinlock (ripretinib):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Qinlock	50 mg	90 tabletter	136.796,40	[redacted]	[redacted]

Prisen er ikke betinget af Medicinrådets anbefaling.

Aftaleforhold

Amgros vil indgå en aftale med leverandøren, som gælder fra den 28.11.2024 til den 30.11.2026. Leverandøren har mulighed for at sætte prisen ned i hele aftaleperioden.

Konkurrencesituationen

Der er på nuværende tidspunkt ingen konkurrence indenfor området. Medicinrådet anbefalede i maj 2024 Ayvakyt (avapritinib) til behandling af inoperabel eller metastatisk gastrointestinal stromal tumor med D842V mutation i PDGFRA. Tabel 2 viser lægemiddeludgiften for Qinlock og Ayvakyt.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Qinlock	50 mg	90 stk	150 mg dagligt	[redacted]	[redacted]
Ayvakyt	300 mg	30 stk.	300 mg dagligt	[redacted]	[redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Ikke anbefalet	Link til anbefaling
England	Ikke anbefalet	Link til anbefaling

Konklusion

[redacted]

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

Color scheme for text highlighting	
Color of highlighted text	**Definition of highlighted text**
	Confidential information

Contact information

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Tables and Figures

Abbreviations

Abbreviation	Definition
2SRC	Two-stage adjustment with recensoring

ADL	Activities of daily living
AE	Adverse event
AIC	Akaike information criterion
ANCOVA	Analysis of covariance
ATC	Anatomical therapeutic chemical
ATP	Adenosine triphosphate
BIC	Bayesian information criterion
BID	Bis in die, twice per day
BICR	Blinded independent central review
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CD117	Cluster of differentiation 117
CEM	Cost-effectiveness model
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIS-fatigue	Checklist Individual Strength Fatigue Severity scale
CR	Complete response
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CWS	Cancer Worry Scale
C2D1	Day one of cycle 2
DCC-2618	Ripretinib
DCO	Data cut off
Df	Degrees of freedom
DK	Denmark

DKK	Danske Kroner / Danish Crowns (currency)
DLQI	Dermatology Life Quality Index
DMC	Medicinrådet / Danish Medicines Council
DOG1	BRCA1-interacting protein 1 (also known as BRIP1)
DRG	Diagnosis-related group
DSA	Deterministic sensitivity analysis
DSD	Dansk Sarkom Databas / Danish Sarcoma Database
DSG	Dansk Sarkom Grupp / Danish Sarcoma Group
DSU	(NICE) Decision Support Unit
EC	European Commission
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EOTRC-BR23	European Organization for Research and Treatment Breast cancer module
EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer Questionnaire
EPAR	European Public Assessment Report
ESMO	European Society for Medical Oncology
EQ-5D(-5L)	EuroQoL Five-Dimension (Five-Level) questionnaire
FACT-Cog V3	Functional Assessment of Cancer Therapy-Cognitive Function-Version 3
FCRI	Fear of Cancer Recurrence Inventory
GIST	Gastrointestinal stromal tumour
HADS	Hospital Anxiety and Depression scale
HR	Hazard ratio
HRQoL	Health-related Quality of Life
HSUV	Health state utility values
HTA	Health technology assessment

ICD	International classification of diseases
ICER	Incremental cost-effectiveness ratio
IES	Impact of Event Scale
IQR	Interquartile range
IPCW	Inverse Probability of Censoring Weights
ITT	Intention to treat
KIT	proto-oncogene c-KIT
KM	Kaplan-Meier
L	Line (of therapy)
LL	Lower limits
MCID	Minimal clinically important difference
MMRM	Mixed model for repeated measurements
MMQ	Maudsley Marital Questionnaire
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
MRI	Magnetic resonance imaging
n	Number
NA	Not applicable
NCT	National clinical trial
NE	Not estimable
NICE	National Institute for Health and Care Excellence
NoMA	Direktoratet for medisinske produkter / Norwegian Medical Products Agency
NR	Not reported
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PBAC	Pharmaceutical Benefits Advisory Committee (Australia)

PBO	Placebo
PD	Progressive disease
PDGFRA	Platelet-derived growth factor reception A
PF	Progression-free
PFS	Progression-free survival
PH	Proportional hazards
PICOS	Population, intervention, comparator, outcome, study design
PR	Partial response
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PRO	Patient-reported outcomes
PROMIS	Patient Reported Outcomes Measurement Information System
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
QALY	Quality-adjusted life year
QD	Quaque die, once daily
QDS	Quater die sumendum, four times a day
QoD	Every other day
QoL	Quality of life
RCT	Randomised control trial
RDI	Relative dose intensity
RNLL	Reintegration to Normal Living Index
RPSFTM	Rank Preserving Structural Failure Time Model
RP2D	Recommended phase 2 dose
RWE	Real-world evidence
SAE	Serious adverse event

SDH	Succinate dehydrogenase
SD	Standard deviation
SE	Standard error
SF-36	36-item short-form health survey
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SPPIC	Self-Perceived Pressure from Informal Care
SSL-D	36-item short-form health survey
S(t)	Probability of survival at time t
TA	Technology appraisal
TDS	Ter die sumendum, three times a day
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
TLV	Tandvårds- och läkemedelsförmånsverket / Swedish Dental and Pharmaceutical Benefits Agency
TTD	Time to treatment discontinuation
UK	United Kingdom
US	United States of America
VAS	Visual analogue scale

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Qinlock
Generic name	Ripretinib
Therapeutic indication as defined by EMA	Qinlock is indicated for the treatment of adult patients with advanced gastrointestinal

	stromal tumour (GIST) who have received prior treatment with three or more kinase inhibitors, including imatinib.
Marketing authorization holder in Denmark	Deciphera Pharmaceuticals (Netherlands) B.V.
ATC code	L01EX19
Combination therapy and/or co-medication	No
(Expected) Date of EC approval	18/11/2021
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	Yes, designated an orphan medicine on 12/10/2017.
Other therapeutic indications approved by EMA	No
Other indications that have been evaluated by the DMC (yes/no)	No
Common Nordic Assessment (JNHB)	Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? [yes/no] Yes Is the product suitable for a joint Nordic assessment? [yes/no] No If no, why not? Ripretinib is not a hospital drug in all of the Nordic countries
Dispensing group	**BEGR**
Packaging – types, sizes/number of units and concentrations	50 mg tablets with a pack size of 90 tablets per bottle.

Abbreviations: ATC: Anatomical Therapeutic Chemical, DMC: Danish Medicines Council, EC: European Commission, EMA: European Medicines Agency.

2. Summary table

Summary

Therapeutic indication relevant for the assessment	Treatment of adult patients with advanced GIST who have received prior treatment with three or more kinase inhibitors, including imatinib – as per EMA indication.
Dosage regiment and administration	150 mg ripretinib orally, once daily.
Choice of comparator	Ripretinib in combination with best supportive care (BSC) is compared with no treatment+BSC.
Prognosis with current treatment (comparator)	Prognosis with current treatment (best supportive care) is that of progressive disease and decreased life expectancy. Median overall survival in advanced GIST patients initiating standard 1L treatment is approximately 57 months (Blanke et al. 2008, DSG 2024a). Median progression free survival for ≥ fourth line (4L) advanced GIST patients treated with best supportive care (BSC) only was 1.0 month in the clinical trial programme for ripretinib (Blay et al. 2020).
Type of evidence for the clinical evaluation	Placebo-controlled clinical trial.
Most important efficacy endpoints (Difference/gain compared to comparator)	**Progression free survival:** ripretinib: 6.3 months (95% CI 4.6-6.9), placebo: 1.0 months (95% CI 0.9-1.7), HR=0.15 (95% CI 0.09–0.25). Disease progression or death (PFS event) occurred in 60% of patients in the ripretinib group (34 [40%] of patients were censored) and in 84% in the placebo group (seven [16%] patients were censored) (Primary data cut 31 May 2019; (Blay et al. 2020)). **Overall survival:** Ripretinib: 15.1 months (95% CI: 12.3 to 15.1), placebo: 6.6 months (95% CI: 4.1 to 11.6), HR=0.36 (95% CI 0.21-0.62) (Primary data cut 31 May 2019; (Blay et al. 2020)). From mature OS data, ripretinib: 18.2 months (95% CI: 13.1 to 30.7), placebo: 6.3 months (95% CI: 0.26 to 10.0). HR=0.41 (95% CI: 0.26 to 0.65) (Data cut 15 January 2021; (von Mehren et al. 2021)). Nonetheless, statistical significance was not able to be tested for OS.
Most important serious adverse events for the intervention and comparator (≥grade 3)	Abdominal pain (ripretinib n=6, placebo n=2), anaemia (ripretinib n=8, placebo n=6), hypertension (ripretinib n=6, placebo n=0)
Impact on health-related quality of life	Patients receiving ripretinib maintained QoL (as assessed by the EORTC QLQ-C30 and EQ-5D-5L PRO measures) from baseline to cycle 2, day 1 whereas QoL declined with placebo, resulting in clinically significant differences between

	treatments (nominal P < 0.01) (Schöffski et al. 2022). EQ-5D-5L VAS: ripretinib: +3.7 (n=70, SD=3.7, 95% CI:-1.1 to 8.6), placebo -8.9 (n=32, SD=19.3, 95% CI:-15.9 to -1.9), Hedges' g=0.62, 95%CI: 0.20 to 1.05) (The Federal Joint Committee (G-BA) 2019, Schöffski et al. 2022) Health economic model: Ripretinib better than comparator.
Type of economic analysis that is submitted	Type of analysis: Cost-utility Type of model: Partitioned survival model
Data sources used to model the clinical effects	INVICTUS clinical trial
Data sources used to model the health-related quality of life	INVICTUS and GRID clinical trials
Life years gained	[redacted]
QALYs gained	[redacted]
Incremental costs	[redacted]
ICER (DKK/QALY)	[redacted]
Uncertainty associated with the ICER estimate	The model assumption with the largest overall impact on the incremental costs and QALY gain is the extrapolation of overall survival
Number of eligible patients in Denmark	Incidence: 60 patients with GIST, of which 40% assumed to be advanced GIST. In total, 11 patients with advanced GIST ≥4L as the relevant patient population Prevalence: 600 patients with GIST
Budget impact (in year 5)	[redacted] DKK

Abbreviations: DKK: Danish Crowns, CI: confidence intervals, EMA: European Medicines Agency, EORTC-QLQ-C30: European Organization for Research and Treatment of Cancer Questionnaire, EQ-5D-5L: EuroQoL Five-Dimension (Five-Level) questionnaire, GIST: gastrointestinal stromal tumour, HR: hazard ratio, ICER: incremental cost-effectiveness ratio, n: number, PRO: Patient reported outcome; QALY: quality-adjusted life-years; QoL: Quality of life.

Source: (Blay et al. 2020, von Mehren et al. 2019, DSD 2023, Søreide et al. 2016, Schöffski et al. 2022, The Federal Joint Committee (G-BA) 2019, [redacted], Zalcberg et al. 2021).

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

On September 17, 2021, a positive opinion was issued by the Committee for Medicinal Products for Human Use (CHMP) to grant marketing authorisation for ripretinib for the treatment of adult patients with advanced gastrointestinal stromal tumour (GIST) previously treated with three or more kinase inhibitors, including at least imatinib (EMA 2021a). Final market authorisation was granted by the European Commission (EC) on November 18, 2021 (EMA 2023c). Reimbursement is sought for the registered indication.

3.1 The medical condition

Advanced GIST is a heterogeneous disease with a complex mutational landscape and poses significant treatment challenges. Advanced GIST in this application refers to metastatic or non-resectable GISTs.

Pathophysiology

Soft tissue tumours, or sarcomas, are malignant tumours in the soft tissues of the body (van Leeuwenhoeck 2023b), which comprise only about 1% of adult malignancies (Gamboa et al. 2020). GISTs are a very rare and heterogenous subtype of sarcoma, with an incidence of 0.4–2 cases per 100 000 per year (Casali et al. 2021, Blay et al. 2010).

Most GISTs arise from genetic mutations in the proto-oncogene c-KIT (KIT) or the platelet-derived growth factor reception alpha (PDGFRA) gene in the cells of Cajal, the “pacemaker cells” of the intestines (Kanker.nl 2022). GIST is a heterogeneous disease that may have various initiating mutations. While KIT (~80%) and PDGFRA (5-10%) are most common, approximately 10-15% GIST patients have wild type mutations (i.e., the disease is not driven by KIT or PDGFRA but by other genetic mutations) (Nishida et al. 2016). The occurrence of these genetic mutations has no obvious cause in most cases and hence there are no known risk factors for the development of GISTs (Internetmedicin 2024). GISTs can occur throughout the gastrointestinal tract but 50-70% of cases originate in the stomach and 20-30% in the small intestine (Wartenberg and Reichardt 2007, Søreide et al. 2016). GISTs can spread through four pathways (Internetmedicin 2024):

- Directly into nearby tissue
- To the liver or other organs via blood from the portal vein (metastases)
- To the abdominal cavity (metastases)
- To the lymphatic system (uncommon)

GISTs almost exclusively metastasize in the liver (Regionala cancercentrum i samverkan 2023), while other organ or systemic metastases remain very rare (Internetmedicin 2024).

GISTs often go undetected in the early stages and about half of the patients already have metastases at diagnosis (Internetmedicin 2024). The diagnosis of GIST is based on the histological appearance of the tumour and mutational analysis (Internetmedicin 2024, DSG 2024a). KIT is detected by immunohistochemical staining for cluster of differentiation 117 (CD117) or the BRCA1-interacting protein 1 (BRIP1/DOG1) gene.

Surgery in combination with (neo)adjuvant treatment with tyrosine kinase inhibitors (TKIs), is the mainstay treatment for localised GISTs (DSG 2024a). In approximately 85% of patients the primary GIST is surgically removable, but around 50% of these patients later develop a recurrence (local or distant) (Reichardt et al. 2013, Ma et al. 2015, Sandvik et al. 2015). Reoperation can then be attempted. For advanced GIST patients, lifelong treatment with TKIs with as few and as short as possible pauses forms standard care (DSG 2024a).

Nonetheless, treatments may spur secondary mutations and induce resistance (DSG 2024a). Secondary mutations in KIT and PDGFRA that drive treatment resistance occur in different exons than primary mutations (Hemming et al. 2018). Secondary KIT mutations are known to arise most commonly in exons 13/14 (the cytoplasmic adenosine triphosphate (ATP)-binding domain) or exons 17/18 (the activation loop), regions that regulate KIT kinase activation (Napolitano and Vincenzi 2019, Hemming et al. 2018). About 3% of all secondary GIST mutations occur on or near the activation loop of PDGFRA (Hemming et al. 2018), generally in exon 18. In vitro experiments recapitulating specific mutations (or combinations of mutations) show dramatic differences in the ability of the currently approved therapies to inhibit tumour growth (Smith et al. 2019). Further support for treatment differences comes from clinical readouts of progression-free survival (PFS) and overall survival (OS) (Heinrich et al. 2003).

Symptoms of the condition

The symptoms of GIST can vary. Patients usually do not experience symptoms from smaller GISTs (≤2 cm), and these are often discovered incidentally (Internetmedicin 2024). Larger tumours can cause symptoms due to mass effect (i.e., internal compression caused by the presence/growth of the tumour) or gastrointestinal bleeding (Internetmedicin 2024). Complaints include nausea, abdominal pain, feeling full, anaemia, diarrhoea, weight loss, decreased appetite, fever, and blood in the stool (van Leeuwenhoeck 2023a, Internetmedicin 2024). Many GIST patients owing to their advanced age also experience comorbidities, including diabetes mellitus, heart failure, cerebrovascular, ischemic heart, and chronic lung disease (Loong et al. 2019).

Patient prognosis

The variability in symptoms is largely due to the different degrees of aggressiveness of the disease. Aggressive forms can spread quickly, produce symptoms early, and metastasize within 1 to 2 years, even despite tumour resection (Miettinen and Lasota 2006, National Comprehensive Cancer Network 2024, Cancerfonden 2023). The severity and likelihood of metastasis is based on the tumour location, size, mutation, relation to surrounding organs,

treatment, and mitotic index (i.e., the ratio of the number of cells in the process of cell division to the total number of cells) (Miettinen and Lasota 2006, National Comprehensive Cancer Network 2024, DSG 2024a). Most recurrences occur in patients deemed high-risk (≥6/5mm^2) by this index (Joensuu et al. 2014). Tumour rupture is also an important indicator for tumour recurrence or metastasis (Joensuu et al. 2014, Casali et al. 2021, Hølmebakk et al. 2019). Tumour rupture or defects to the tumour integrity can occur spontaneously or during surgical manipulation and include tumour fracture or spillage, gastrointestinal perforation at the tumour site, and microscopic infiltration of the tumour of an adjacent organ (Nishida et al. 2019).

A study of patients with operable GISTs showed differences in prognosis by GIST location: stomach had the best prognosis, followed by the small and large intestine, oesophagus and lastly extra gastrointestinal GISTs (Joensuu et al. 2012). They had five-year recurrence-free survival rates of 88%, 63%, 60%, and 40%, respectively (Joensuu et al. 2012). Whereas high-risk GIST patients have a median time to recurrence of around two years (National Comprehensive Cancer Network 2024).

Survival has improved since the introduction of the first TKI (DSG 2024a). The five-year relative survival for all GIST patients in Norway 2013-2022 of 90.5% indicates survival with today's standard of care for all GIST patients, including resectable tumours with a low risk of recurrence (Kreftregisteret 2023). For advanced GIST, there has been an observed improvement in median OS in advanced GIST patients from approximately 20 months (DeMatteo et al. 2000) to 57 months (Blanke et al. 2008, DSG 2024a).

Quality of Life (QoL) and impact on daily life

Both having a GIST and being treated for one can negatively affect a patient's health-related quality of life (HRQoL) (Fauske et al. 2019). In many cases, the GIST diagnosis and fear of tumour progression may lead to mental health problems (Fauske et al. 2019, van de Wal et al. 2022, Custers et al. 2015). In addition, (repeated) surgeries to remove the tumour can cause abdominal pain, dumping syndrome, and food intolerances (Fauske et al. 2019). A study using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EOTRC-QLQ-C30) showed that GIST patients scored lower than the general German population on almost all functional domains, including role, emotional, cognitive, and social functioning (Eichler et al. 2021). GIST patients also had significantly higher scores for symptom domains, namely fatigue, nausea, insomnia, decreased appetite, constipation, diarrhoea, and financial problems. Accordingly, patients with GIST have lower HRQoL than the general population (Eichler et al. 2021).

Quality of life (QoL) and patient functioning is increasingly impaired as the disease progresses. Lower HRQoL is evidenced among GIST patients undergoing treatment with currently available TKIs owing to side effects (van de Wal et al. 2022). The German study described above also found that HRQoL worsened across all functional domains among patients having ≥2L therapy (Eichler et al. 2021).

Unmet need

GISTs are insensitive to traditional chemotherapy (DSG 2024a). Despite imatinib revolutionising GIST treatment in early 2000s, most patients still experience disease progression after 2-3 years on imatinib due to the emergence of secondary kinase mutation as explained above. This process continues to be repeated in the subsequent lines of treatment now available, resulting in multiple secondary mutations and more extensive resistance to therapy. The existing GIST therapies are often unable to effectively treat tumours with these secondary mutations given their single mode of action (Hemming et al. 2018). This leaves a clear unmet need for patients suffering from advanced GIST, who need a drug with broad inhibition capacity to lower eventual disease progression and a manageable toxicity profile.

Ripretinib is an innovative TKI developed specifically for GISTs with a unique dual mechanism of action that regulates both the kinase switch pocket and the kinase activation loop. It is an effective and well tolerated inhibitor of KIT and PDGFRA primary and secondary mutations, delaying disease progression in advanced GIST. The 2024 updates to the Dansk Sarkom Gruppe (DSG) treatment guidelines place ripretinib as the 4L treatment in Denmark, in line with international recommendations (DSG 2024a, Casali et al. 2021). However, without reimbursement there is uncertain and unequal access to this therapy for this patient group.

3.2 Patient population

3.2.1 Gist epidemiology

GISTs often develop between the 55th and 65th years of life, and, although GISTs also occur in adults under 40 or adolescents and children, they are very rare in this population (Wartenberg and Reichardt 2007, Miettinen and Lasota 2006). A systematic literature review (SLR) found that the age at GIST diagnosis ranged from 10 to 100 years, with the median age being mid 60s across studies (Søreide et al. 2016). The gender distribution has a fairly consistent equal distribution across studies between male and females (Søreide et al. 2016), although slightly more males with GIST are in clinical practice ([redacted]).

The lack of a GIST-specific International Classification of Diseases (ICD) code hinders register-based studies. Accordingly, medical records or disease-specific clinical registers are required to estimate the incidence and prevalence of this rare disease.

The global incidence of GIST is approximately 10-15 cases per million (Søreide et al. 2016). Variation in reported incidence is largely methodological, owing to developing diagnostic criteria and improved diagnostics over time as well as differences in data capture (Søreide et al. 2016). Any reported increased incidence is more often among the very low to intermediate risk tumours and not noticeable in clinical practice ([redacted]). In 2022, 60 GIST patients had their first contact at a Danish sarcoma clinic (DSD 2023). Accordingly, an annual incidence of 60 GIST patients is assumed, highlighting the rarity of GIST in a population of 5 965 990 (Statistics Denmark 2024).

The prevalence of GIST patients is suggested to be over ten times that of the incidence for all GIST (Søreide et al. 2016). Thus, the prevalent patient population is assumed to be ten-fold that of the annual incident population (600 patients).

The estimated incidence and prevalence of GIST patients in Denmark is presented in Table 1 based on the annual incidence from the Danish Sarcoma Database (DSD) and a prevalence that is ten-fold that of the incidence (DSD 2023, Søreide et al. 2016). These estimates of the incidence and prevalence are for all GISTs, and not only advanced GISTs comprising patients with unresectable tumours or metastatic disease who are relevant for the current application. There is also an assumption of stability in diagnoses over the past five years, in line with Danish clinical experience ([redacted]).

Table 1 Incidence and prevalence in the past 5 years (Denmark)

Year	2019	2020	2021	2022	2023
Incidence	60	60	60	60	60
Prevalence	600	600	600	600	600

Source: (DSD 2023, Søreide et al. 2016).

3.2.2 Advanced GIST ≥4L therapy patient population

The indication for ripretinib is for the treatment of adult patients with advanced GIST previously treated with three or more kinase inhibitors, including imatinib (EMA 2023b). This population matches the patient population from the Phase 3 Study of DCC-2618 vs Placebo in the clinical trial named Advanced GIST Patients Who Have Been Treated With Prior Anticancer Therapies (INVICTUS) (NCT03353753). This trial investigated the efficacy and safety of ripretinib among patients whom had been previously treated with three or more lines of therapy (ClinicalTrials.gov 2022).

Ripretinib, being a ≥4L therapy for advanced GIST, is estimated to have an eligible patient population in the range of two to three patients per million of the general population ([redacted]). There is uncertainty with the exact proportion of GIST patients who are deemed to have advanced GIST whether due to metastases at diagnosis, recurrence, or unresectable nature of their tumours, as well as one that is imatinib sensitive. A Danish clinical expert has estimated that perhaps only 25% of all GIST patients meet this definition of advanced, although some would also have other mutations and have different 1L treatments (Deciphera 2024d). Hence for simplification, we have assumed that of the 60 incident GIST patients (DSD 2023), that 40% (n=24) of these patients have advanced GIST but all of these patients are treated 1L imatinib specifically.

The flow of advanced GIST patients across lines of therapy have been estimated using GIST patient data from the regorafenib "GRID" clinical trial (Demetri et al. 2013) ([redacted]). Data was taken from GRID to estimate the percentage change across the therapeutic lines except for the change from 3L which is informed by Dutch patient population data which is assumed to be like the Danish patient population. This flow of patients has also been validated by a Danish clinical expert as reflecting clinical practice (Deciphera 2024d). The proportions advancing to 3L and 4L treatment are likely lower end

boundaries in Danish clinical practice and further illuminate the unmet need for an effective treatment with a manageable toxicity profile for these patients ([redacted]). Ultimately, from the advanced GIST patient population, eleven patients are estimated to be eligible for ≥4L treatment with ripretinib in Denmark in a given year ([redacted]). Thus, placing as the lower bound of the estimated range of two to three patients per million of the general population, resulting in an approximate range of 12 to 18 advanced GIST patients per year in Denmark ([redacted], Statistics Denmark 2024).

Figure 1 [redacted]

Abbreviations: GIST: Gastrointestinal stromal tumour.
Source: Adapted from data on file: ([redacted]).

The estimated ≥4L patient population relevant for treatment with ripretinib is not expected to increase over the next five years ([redacted]) (See Table 2).

Table 2 Estimated number of patients eligible for treatment (Denmark)

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Patients (n)	11	11	11	11	11

Abbreviations: n: number.

3.3 Current treatment options

3.3.1 European treatment guidelines

European Society for Medical Oncology (ESMO) and partners have produced clinical guidelines for the diagnosis, treatment, and follow up of GISTs (Casali et al. 2021). Diagnosis of GIST includes imaging, biopsy, genotyping, and assessment for possible surgical resection. GISTs can be resectable or unresectable. Surgical resection is the first choice for resectable GISTs without metastasis, and administration of TKIs is the primary approach for unresectable, metastatic, or recurrent GISTs (EMA 2021a). Treatment of GIST at the earliest stage with surgical resection is highly effective, but surgical resection is not

possible in approximately 15% of patients, and recurrence and/or metastases occur in approximately 50% of patients (Trent and Subramanian 2014).

For advanced GIST where tumour resection is not feasible or metastatic GIST, the treatment algorithm is summarised in Figure 2. The treatment algorithm of advanced GIST, consists of continuous systemic anticancer therapy with TKIs (Casali et al. 2021). The available TKIs in the algorithm act on different receptors, hence the algorithm is divided into whether the tumour is imatinib sensitive or not. Accordingly, mutational analysis is highly important for decision making (Reichardt et al. 2012). The focus below is on the imatinib-sensitive tumours owing to the label of ripretinib requiring three or more TKIs, including imatinib (EMA 2023b).

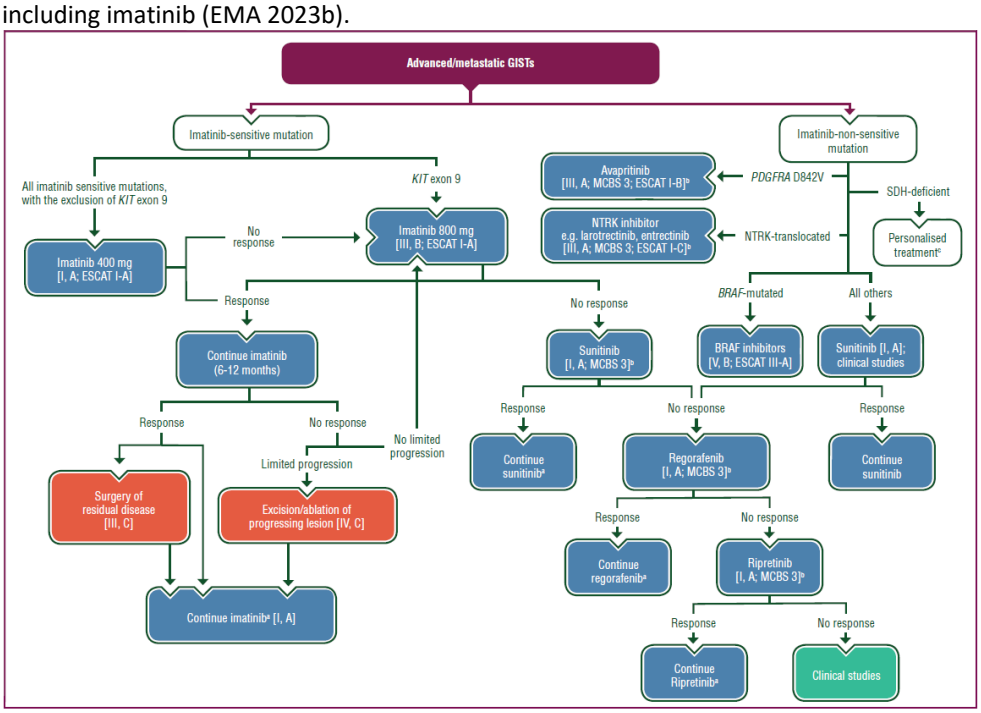


Figure 2 ESMO's treatment algorithm for advanced/metastatic GISTs

Abbreviations: GIST: Gastrointestinal stromal tumour.
Source: ESMO (Casali et al. 2021).

Imatinib is the 1L for imatinib-sensitive tumours. A dose increase with imatinib is possible if no response on the initial dose for patients with imatinib sensitive mutations with the exclusion of KIT exon 9 who initiate on the higher dose. When insufficient response is observed or the patient shows intolerance to treatment, treatment will be discontinued and treatment with sunitinib will be started as 2L. Treatment with sunitinib will also continue until an inadequate response is observed or the patient shows intolerance. Regorafenib constitutes 3L. Here, the same guidelines regarding the duration of treatment apply, namely, as long as benefit is observed or until unacceptable toxicity occurs (Sundhed.dk 2022, EMA 2023d, Deciphera 2024d).

Patients progressing on imatinib, sunitinib, and regorafenib tend to have a complex and heterogeneous mutational landscape. In the 4L, ESMO recommends ripretinib (Casali et

al. 2021, National Comprehensive Cancer Network 2024). Ripretinib was included in the ESMO guidelines as the only treatment option for 4L patients already at the time of its approval in Europe owing to its unique mechanism of action to close the treatment gap after failure of 3L therapy (Casali et al. 2021, National Comprehensive Cancer Network 2024). No other specific agents are currently recommended by ESMO for ≥4L.

In addition to TKIs that are used to actively address the disease, patients, mainly in the later lines of treatment, also receive best supportive care (BSC). BSC consists of agents that try to maintain the patient's QoL as much as possible, for example, to manage cancer pain or other GIST complications (Fallon et al. 2018).

Continuous lifelong treatment with TKIs with as few and as short as possible pauses between lines, forms the basis of clinical practice for advanced GIST patients today (DSG 2024a, Casali et al. 2021). Throughout the treatment algorithm, a break or interruption in TKI treatment can usually lead to rapid tumour progression. Hence it is important to assess the patient's compliance and to optimally handle side effects (Casali et al. 2021).

3.3.2 Danish treatment guidelines

In Denmark, the treatment of sarcomas is coordinated by the DSG (Kræftens Bekæmpelse 2024, DSG 2024b). Sundhed.dk has GIST-specific guidelines from 2022 (Sundhed.dk 2022) which directly refer to the ESMO guidelines (Casali et al. 2021). In addition, DSG also have recently produced updated GIST treatment guidelines that recommend ripretinib (DSG 2024a). In Danish clinical practice there is no deviation from ESMO's treatment algorithm up until 4L, where the recommended treatment ripretinib is not currently reimbursed. [redacted] ([redacted]). The sundhed.dk guidelines cite an estimated average survival time for patients with GIST of be 31 months (Sundhed.dk 2022). However, they note that while 31-50% of patients who had GIST resections are alive at 10 years, the prognosis deteriorates with metastatic GIST.

Medical treatment is considered to be lifelong for advanced GIST (DSG 2024a). Medical treatment is provided if the GIST is inoperable or metastatic through two national sarcoma centres (Copenhagen and Aarhus) (Kræftens Bekæmpelse 2024). Before starting medical treatment, tumour mutation analyses should be conducted for KIT and PDGFRA (DSG 2024a). Below follows the Danish guidelines for imatinib-sensitive tumours. Imatinib, sunitinib and regorafenib are available and well established in Denmark (DSG 2024a). Clinical benefit of the above treatments is assessed in the clinic as a composite of several factors including speed of progression, symptoms, and changes in QoL ([redacted]). These treatments are all approved and consistent with the ESMO guidelines.

Imatinib comprises the 1L of treatment for most advanced GIST-patients (Sundhed.dk 2022, Herlev Hospital 2024, Kræftens Bekæmpelse 2024, DSG 2024a). Imatinib 400 mg daily is to be offered as long as it is tolerable and as long as the disease is controlled (Herlev Hospital 2024, DSG 2024a). Upon progression with imatinib 400 mg daily a dose escalation to 400 mg twice daily can be attempted (DSG 2024a). For patients with mutations in KIT exon 9, 800 mg should be the initial dose (DSG 2024a). Median OS of advanced GIST

patients has been observed to increase from approximately 20 to 57 months with the introduction of imatinib (DSG 2024a).

Second-line treatment is with sunitinib (Herlev Hospital 2024, Kræftens Bekæmpelse 2024, DSG 2024a). Sunitinib is given in tablet form in a six-week treatment cycle. Starting dose is 50 mg once a day for four weeks followed by a two-week break (EMA 2021b). The dose can be individually adjusted between 25 and 75 mg as per label. A constant dose of 37.5 mg a day may be used as instead of intermittent treatment (DSG 2024a).

Third-line treatment is with regorafenib (DSG 2024a, Herlev Hospital 2024). This takes place in cycles of four weeks: once daily for three weeks followed by a 1-week break. Throughout treatment with regorafenib, regular blood pressure measurements and blood and urine tests are conducted (Herlev Hospital 2024). In addition, a CT scan of the lungs and abdominal cavity is conducted approximately every three months (Herlev Hospital 2024). Treatment should continue with regorafenib as long as there is benefit or until unacceptable toxicity occurs (EMA 2023d). Severe side effects or blood test results may also lead to pauses in treatment or reduced doses (Herlev Hospital 2024).

The recently updated DSG guidelines recommend ripretinib, 150 mg daily as the 4L treatment upon progression and or intolerance to imatinib, sunitinib and regorafenib, based on the results of clinical trials including INVICTUS and in line with ESMO recommendations (DSG 2024a). The guidelines suggest accessing ripretinib through Regional Medicines Committee (Regionale Lægemiddelkomite) given the current reimbursement status (DSG 2024a). In lieu of the availability of ripretinib however, the choice of 4L treatment in clinical practice remains highly individualised, considering the patients' health status and mutational status (DSG 2024a, Deciphera 2024d).

There are several off-label treatment options to achieve lifelong continuous treatment after exhausting recommended treatments. The DSG guidelines state that the following treatments can be considered (in no particular order) after progressing or not tolerating the four approved treatments: sorafenib, nilotinib, pazopanib, avapritinib, cabozantinib, ponatinib, dose escalation of ripretinib, as well as everolimus in combination with imatinib (DSG 2024a). Many of which are used as 4L treatment today due to the lack of ripretinib availability with Herlev Hospital providing patient information on sorafenib and nilotinib (Herlev Hospital 2024). For sorafenib, the recommendation is based on only phase II trials for GIST patients and observational data indicating the need for dose reduction in a third of patients (DSG 2024a). Evidence for nilotinib is largely assessing use as 3L treatment for advanced GIST with median PFS and OS just below that what is found for studies investigating regorafenib (DSG 2024a). After exhausting possible active agents, the DSG guidelines recommend attempting TKI rechallenge by the re-introduction of imatinib 400 mg (DSG 2024a). Yet, this is based on a single clinical trial which found only limited PFS advantage to placebo (Kang et al. 2013). Thus, underpinning that these are off-label agents with limited clinical evidence for use in advanced GIST at this line of treatment.

Overall, the overarching treatment recommendation for Danish patients with advanced GIST is that of continuous treatment with TKIs with the fewest and shortest possible breaks with EMA approved treatments from 1L to ripretinib at 4L. Importantly, ripretinib is named as the only recommended 4L treatment for advanced GIST patients.

3.4 The intervention

Ripretinib is an innovative TKI developed specifically for GIST tumours. Ripretinib is an effective and well tolerated inhibitor of KIT and PDGFRA primary and secondary mutations delaying disease progression in unresectable advanced GIST. Table 3 contains a brief description of ripretinib (EMA 2023b).

Ripretinib has a unique dual mechanism of action that regulates both the kinase switch pocket and the kinase activation loop. Through binding to the kinase, signalling is prevented, and cell multiplication is halted. Given its dual mechanism of action, ripretinib has a wide range of inhibition and appears to be effective for both the most common primary and secondary mutations (KIT and PDGFRA mutated kinases) (Smith et al. 2019). Ripretinib also inhibits other kinases in vitro, including PDGFRB, TIE2, VEGFR2 and BRAF (EMA 2023b). The toxicity of current later-line therapies can make them difficult to tolerate, with many patients requiring dose adjustments or treatment interruptions, contributing to their progression through the available options (Zalcberg et al. 2021). Until the approval of ripretinib, no approved drugs were available for patients with advanced GIST who have previously received treatment with three or more TKIs, including imatinib. Accordingly, ripretinib addresses the significant unmet medical need for GIST patients who historically have had limited treatment options, after progressing through multiple lines of TKIs by providing a treatment option which inhibits a broad range of primary and secondary mutations.

Ripretinib should be taken every day at the same time with or without food. The treatment is in tablet form and can be taken within the patients' home. Furthermore, treatment with ripretinib should be continued as long as medical benefit is observed or until unacceptable toxicity occurs (EMA 2023b).

Table 3 Overview of the intervention | Qinlock (ripretinib)

Overview of intervention	Qinlock (ripretinib)
Therapeutic indication relevant for the assessment	Treatment of adult patients with advanced GIST who have received prior treatment with three or more kinase inhibitors, including imatinib
Method of administration	Oral administration (tablet form) with or without food
Dosing	The recommended dose is 150 mg ripretinib (three 50 mg tablets) taken once daily at the same time each day with or without food. Dose interruptions or reductions may be required based on individual safety and tolerability
Dosing in the health economic model (including relative dose intensity)	Dosing: 150 mg once daily Relative dose intensity: 96.5%
Should the medicine be administered with other medicines?	No required concomitant medicines

Treatment duration / criteria for end of treatment	Treatment with Qinlock should continue as long as benefit is observed or until unacceptable toxicity
Necessary monitoring, both during administration and during the treatment period	None. Close monitoring of overall efficacy and safety is recommended in patients also taking CYP3A inducers, suffering from hepatic impairment, or from hypertension
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	No specific diagnostics required for initiating ripretinib. One-off costs for initiating ripretinib are included in the model: imaging (MRI/CT), full blood count and liver function tests
Package size(s)	90 x 50 mg tablets per package

Abbreviations: GIST: Gastrointestinal stromal tumour, MRI: Magnetic resonance imaging, CT: Computed tomography.

Source: Qinlock Summary of Product Charateristics (EMA 2023b).

3.4.1 The intervention in relation to Danish clinical practice

Ripretinib is expected to be used as a ≥4L therapy in adults diagnosed with advanced GIST, who have received prior treatment with at least three kinase inhibitors, including imatinib.

As detailed in Chapter 3.3, the treatment algorithm for GISTs is divided according to whether the mutation is imatinib-sensitive or not. For imatinib-sensitive mutations, 1L treatment consists of imatinib followed by increased doses. Second-line treatment consists of sunitinib, followed by regorafenib as 3L. Ripretinib does not alter the treatment algorithm as it first comes in as a 4L treatment option where there were previously no approved active treatments available. No specific diagnostics are required for initiation as the drug is indicated only following lack of response or tolerability to previous treatments.

3.5 Choice of comparator(s)

As described in Chapter 3.3, no approved active treatment is currently available in the ≥4L for advanced GIST patients. The guidelines specify ripretinib as the recommended treatment for 4L (DSG 2024a). The off-label treatments mentioned in the guidelines for >4L have not been assessed for cost-effectiveness in this patient population. Today, upon discontinuation of regorafenib at 3L, highly individualised treatment decisions are made in clinical practice based on guidelines, clinician experience, and patient health status (Deciphera 2024d). Hence there is no active treatment comparator applicable to this case, and consequently the most relevant comparison to determine the cost-effectiveness of ripretinib in advanced ≥ 4L GIST is ripretinib + BSC vs. no active treatment + BSC.

BSC in this context consists of non-disease-specific agents that aim to provide GIST patients comfort and QoL. Patients with GIST often take several medications to handle potential GIST symptoms and progression-related complications. The agents which help manage GIST symptoms were sourced from those reported in the INVICTUS trial

([redacted]) and have been validated as comprising BSC in Danish clinical practice ([redacted]).

The INVICTUS study compared ripretinib to placebo in advanced GIST patients previously treated with the standard treatment algorithm (i.e., imatinib, sunitinib, regorafenib) (Blay et al. 2020). When the effectiveness of ripretinib versus placebo is discussed in this dossier, it means the effectiveness of the addition of ripretinib to BSC versus BSC alone without an active treatment to the underlying disease. Table 4 contains an overview of the comparator of no active treatment for the underlying disease.

Table 4 Overview of the comparator | Best supportive care

Overview of comparator	(Best supportive care – not a single pharmaceutical)
Generic name	NA
ATC code	NA
Mechanism of action	NA
Method of administration	NA
Dosing	NA
Dosing in the health economic model (including relative dose intensity)	NA
Should the medicine be administered with other medicines?	NA
Treatment duration/ criteria for end of treatment	NA
Need for diagnostics or other tests (i.e. companion diagnostics)	NA
Package size(s)	NA

Abbreviations: ATC: Anatomical Therapeutic Chemical, NA: Not applicable.

3.6 Cost-effectiveness of the comparator(s)

Not applicable.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

The INVICTUS trial is the pivotal study in the direct comparison of adding ripretinib to BSC versus placebo with BSC for ≥4L advanced GIST. The primary efficacy endpoint was PFS

according to mRECIST (Modified Response Evaluation Criteria in Solid Tumors) 1.1, as assessed by a blinded independent central review (BICR) (Blay et al. 2020, ClinicalTrials.gov 2022). Key secondary endpoints included: objective response rate (ORR, confirmed complete response and partial response assessed by BICR), OS, and HRQoL. These measures were considered most appropriate due to their applicability to terminal diseases as well as their frequent use in efficacy studies of similar treatments and indications. They provide a clear and comparable measure of the impact of ripretinib on outcomes relevant for both practitioners and patients. All efficacy endpoints included in the application are in Table 5. Additional measures and definitions thereof are available on ClinicalTrials.gov (ClinicalTrials.gov 2022).

Validity of outcomes

The European Medicines Agency (EMA) recommends that registration studies should be able to demonstrate that the drug provides a clinical benefit in terms of survival (EMA 2019). EMA considers OS and PFS to be acceptable primary outcome measures in Phase 3 studies. In addition, EMA indicates that when PFS is the primary endpoint, OS should be included as a secondary endpoint and vice versa. Regardless of the choice of primary endpoint, ORR and duration of response should also be included in the evaluation. Furthermore, it is important to include endpoints that measure HRQoL as such endpoints provide insight into the patient's experience with the disease and treatment. Finally, the safety profile of treatment arms should be included in the evaluation. INVICTUS was designed to meet these requirements (ClinicalTrials.gov 2022).

The primary efficacy endpoint of the INVICTUS trial was PFS (the interval between the date of randomisation and the date of disease progression or death) as measured by a BICR. Although PFS in the INVICTUS study was also measured by investigators, only the PFS measured by BICR is presented. PFS captures improvement in symptoms and the associated improvement in the QoL of patients through the response, including the prevention or delay of progression of the disease, an event with drastic consequences for patients. The knowledge that a drug is capable of causing a delay in progression or disease stabilisation is of great value to a patient and so PFS and response rates are recognised as patient-relevant endpoints by both European and American regulatory guidelines (U.S. Department of Health and Human Services Food and Drug Administration (FDA) 2018, EMA 2019). PFS has also been reported in efficacy studies of imatinib (Gastrointestinal Stromal Tumor Meta-Analysis Group (MetaGIST) 2010) and regorafenib (EMA 2023d) in advanced GIST as a primary endpoint. In addition, even stabilising the disease represents a significant success within this line of therapy for seriously ill patients and is associated with high patient satisfaction and relevance. Delaying progression, including stabilising the disease (stopping progression), while maintaining good tolerability is the primary treatment goal within the 4L setting.

In line with EMA recommendations, OS (the time between randomisation and death from any cause) was added as a secondary endpoint given the choice of PFS as the primary endpoint in INVICTUS. OS informed the model on all-cause mortality, a patient-relevant and directly measurable endpoint in advanced GIST. Due to the significantly different mean observation times during the double-blind phase in the two study arms (primary

data cutoff: ripretinib: 26.1 weeks, placebo: 9.6 weeks), survival time analyses of PFS and OS based on the hazard ratio (HR) are used to derive the additional benefit of ripretinib.

The other efficacy outcomes such as ORR and safety were also measured, showing that in addition to achieving complete or partial response, maintaining stable disease with minimal side effects is also a valuable patient-relevant endpoint in the treatment of GIST.

Table 5 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Progression-free survival (PFS) NCT03353753 Primary endpoint in INVICTUS	Baseline to end of study. Once at screening, then every cycle (28 days) for four cycles, and then every other cycle. Time points reported: Primary analysis data cut-off after 90 PFS events have occurred (31 May 2019). Data cut 15 January 2021.	The interval between the date of randomisation and the earliest documented evidence of the first disease progression based on the independent radiologic review or death due to any cause on initially assigned study treatment, whichever comes earlier.	Tumour assessments were done using CT scans (or MRI scans in case of contrast media allergy) with independent radiologic review. This primary endpoint was estimated in the ITT population. Analysis for PFS was stratified by the randomisation stratification factors [prior lines of therapy (3 versus ≥4) and ECOG (0 versus 1 or 2)]. The p-value was from a two-sided stratified Log-rank test. Point estimates as hazard ratios were obtained from a Cox regression model with treatment and the randomisation stratification factors as fixed factors. 95% CI were obtained using Wald method. PFS time was summarized via KM methodology using the 25th, 50th (median), and 75th percentiles and pre-specified timepoints, each with associated two-sided 95% CIs.
Overall survival (OS) NCT03353753 Secondary endpoint in INVICTUS	Baseline to end of study. Assessed every three months from enrolment. Time points reported: Primary analysis data cut-off (May 2019). Data cut 15 January 2021.	The interval between the date of randomisation until the date of death from any cause or the date of last follow-up.	Patients were contacted by phone to collect long-term overall survival data. OS was estimated in the ITT population with similar methods as with PFS.
Objective response rate (ORR)	Baseline to end of study.	The proportion of patients with a confirmed CR or PR based on the	Assessed by blinded independent central review.

NCT03353753 Secondary endpoint in INVICTUS	Time point reported: Primary analysis data cut-off (May 2019).	independent radiologic review and during the initial assigned study treatment.	Performed in the ITT-population as the main analysis. To be assigned a status of a CR or PR, changes in tumour measurements were confirmed by repeat assessments that were performed at least four weeks (allowing a minus three days window). After the criteria for response are first met. This analysis included assessments prior to an event or censoring under the primary PFS analysis. Patients with unknown or missing response were categorised as non-responders and were included in the denominator when calculating the proportion. An unstratified two-sided Fisher's Exact test at a 0.05 significance level was used. A 95% Newcombe score CI was constructed for the treatment rate difference in ORR.

* Time point for data collection used in analysis (follow up time for time-to-event measures)

Abbreviations: CI: Confidence interval, CR: complete response, CT: Computed tomography, ECOG: Eastern Cooperative Oncology Group, ITT: Intention to treat, KM: Kaplan Meier, MRI: Magnetic resonance imaging, PR: Partial response, PFS: Progression-free survival.

Source: (ClinicalTrials.gov 2022, Blay et al. 2020).

4. Health economic analysis

4.1 Model structure

Partitioned survival models (PSMs) have been extensively used to model oncology treatments. In a review by NICE covering May 2013 to February 2016, it was found that 73% of 30 oncology appraisals evaluated by NICE used a PSM (Woods et al. 2017).

A review of the use of partitioned survival analysis in recent technology appraisals (TAs) of cancer treatments found similar criticisms between the use of PSMs and Markov models. Although the Markov structure allows for more flexibility to model complex disease trajectories, it has additional data requirements than PSMs. Further model structures have been accepted during health technology assessment (HTA), including time-in-state and cumulative survival models, although these are rarely used.

A PSM structure was selected since the data requirements for partitioned survival analysis are fulfilled by the clinical trial endpoints in INVICTUS. The model was developed in Microsoft Excel®. The model includes three disease-related health states: progression-free (PF), progressed disease (PD), and death. To capture the effect of patients remaining on ripretinib treatment after progression, the PD state is then further divided into PD on treatment and PD off treatment.

In a typical three-state PSM, the distribution of patients between the PF, PD and death health states are estimated over time based on survival curves (Figure 3A). The OS and PFS curves are combined to estimate the proportion of patients PF, with PD and death, where S(t) is the probability of survival beyond time t. The area-under-the-curve approach is then used to estimate the time patients spend in the PF and PD states. In the ripretinib cost-utility model, clinicians reported that it would be important to include the effects of continued treatment after disease progression. This phenomenon was therefore captured by dividing the PD state into two sub-states: on treatment and off treatment (Figure 3B). BSC is modelled according to praxis. [redacted] ([redacted]).

Figure 3 [redacted]

Abbreviations: OS: Overall survival, PFS: Progression-free survival, S(t): probability of survival at time t, TTD: Time to treatment discontinuation.

4.2 Model features

Table 6 summarises the features of the economic model.

Table 6 Features of the economic model

Model features	Description	Justification
Patient population	Adult patients with advanced GIST who have had prior therapy with at least three kinase inhibitors, including imatinib.	According to EMA approval and label.
Perspective	Limited societal perspective.	According to DMC guidelines.
Time horizon	Lifetime (40 years)	To capture all health benefits and costs in line with DMC guidelines. Based on mean age at diagnosis in the Danish population in mid 60s (Deciphera 2024d).
Cycle length	28 days	Consistent with length of treatment cycle (day one every 28 days).

Half-cycle correction	Yes	
Discount rate	3.5 %	The DMC applies a discount rate of 3.5 %.
Intervention	Ripretinib + BSC	
Comparator(s)	BSC alone	Ripretinib is the sole recommended 4L treatment today (DSG 2024a). There is currently no approved and reimbursed active treatments available for ≥4L treatment with any active treatments in clinical practice being rechallenges or off-label.
Outcomes	OS, PFS, TTD, HRQoL	

Abbreviations: BSC: Best supportive care, DMC: Danish Medicines Council, GIST: Gastrointestinal stromal tumour, HRQoL: Health-related quality of life, OS: Overall survival, PFS: Progression-free survival, TTD: Time to discontinuation.

5. Overview of literature

5.1 Literature used for the clinical assessment

The present application is based on the pivotal Phase III clinical trial for the efficacy and safety of ripretinib, INVICTUS, which directly compared the addition of ripretinib to BSC to a placebo (i.e. no active treatment) alongside BSC as ≥4L therapy among advanced GIST patients (ClinicalTrials.gov 2022). No other trial with the relevant BSC + placebo comparator group was identified pertaining to this drug (ripretinib), comparison (no active treatment), and patient group (≥4L advanced GIST). The relevant publications from INVICTUS trial used in this application are listed in Table 7. An SLR detailed in Appendix H was conducted to ensure an exhaustive review of relevant literature and increase understanding of the treatment landscape for advanced GIST. The relevant publications used for the clinical assessment include the two records identified in the efficacy SLR. In addition, clinical study reports for the primary data analysis and the later data cut off January 15, 2021 have been utilised in this application ([redacted]) as well as post hoc time to discontinuation analyses ([redacted]).

Table 7 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
BLAY, J. Y., et al. 2020. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol, 21, 923-934. VON MEHREN, M., et al. 2021. Ripretinib as ≥4L treatment in patients with advanced gastrointestinal stromal tumour: Long-term update from the phase III INVICTUS study. Annals of Oncology, 32, S1120-S1121. ZALCBERG, J. R., et al. 2020. 1622MO Clinical benefit with ripretinib as ≥4th line treatment in patients with advanced gastrointestinal stromal tumors (GIST): Update from the phase III INVICTUS study. Annals of Oncology, 31, S973-S974.	INVICTUS	NCT03353753	Start: 27/02/2018 Completion: 31/05/2022 Data cut-off (primary endpoint analysis): 31/05/2019 Additional follow up cut-offs: 10/08/2020 15/01/2021 End of study: 11/05/2022	Oral ripretinib 150mg once daily vs. placebo for patients with advanced GIST who have progressed on imatinib, sunitinib, and regorafenib or have documented intolerance to any of these treatments.

* If there are several publications connected to a trial, include all publications used.

Abbreviations: GIST: Gastrointestinal tumours, NCT: National clinical trial.

5.2 Literature used for the assessment of health-related quality of life

The impacts on HRQoL associated with ripretinib were thoroughly investigated through a SLR as detailed in Appendix I. The relevant publications for HRQoL outcomes are presented in Table 8. The present application is primarily based on the pivotal Phase III clinical trial for the efficacy and safety of ripretinib, INVICTUS, which compared the addition of ripretinib to BSC to a placebo alongside BSC. Given the publication by Schöffski and colleagues (Schöffski et al. 2022) only reported the VAS and EOTRC-QLC-30 data, INVICTUS data was used to derive the relevant health state utility values with Danish utility weights specifically for this application. In addition, utility for the health state, progressed disease off treatment, was derived from a publication from the GRID trial, identified through the SLR as relevant for advanced GIST patients who have progressed and no longer remain on treatment (Poole et al. 2015).

Table 8 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
SCHÖFFSKI, P., et al., 2022. Patient-reported outcomes in individuals with advanced gastrointestinal stromal tumor treated with ripretinib in the 4L setting: analysis from the phase 3 INVICTUS trial. BMC Cancer, 22, 1302.	No index utilities contained. Reference provided VAS scores and disease-specific instrument for ≥4L advanced GIST patients	See Section 10.1 and Appendix F
POOLE, C. D., et al., 2015. Health utility of patients with advanced gastrointestinal stromal tumors (GIST) after failure of imatinib and sunitinib: findings from GRID, a randomized, double-blind, placebo-controlled phase III study of regorafenib versus placebo. Gastric Cancer. 18(3):627-634	Progressed disease (off treatment) utility: 0.65	See Section 10.3

Abbreviations: GIST: Gastrointestinal stromal tumour, L: Line of therapy, VAS: Visual analogue scale.

5.3 Literature used for inputs for the health economic model

An SLR was conducted to ensure a complete understanding of the health economic aspects of ripretinib as detailed in Appendix J. Additional information was sourced for the health economic model through targeted literature searches and desk research, this included the disutility values for the included adverse events (AEs). The relevant sources identified and utilised in the model are detailed in Table 9.

Table 9 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
DOYLE, S., LLOYD, A. & WALKER, M. 2008. Health state utility scores in advanced non-small cell lung cancer. Lung Cancer, 62, 374-80.	Disutility values for abdominal pain and hypertension.	Desk review of previous NICE submissions and then reference list scanning.	See Section 10.3.4
HARROW, B. S., EATON, C. B., ROBERTS, M. B., ASSAF, A. R., LUO, X. & CHEN, Z. 2011. Health utilities associated with haemoglobin levels and blood loss in postmenopausal women: the Women's Health Initiative. Value Health, 14, 555-63.	Disutility value for anaemia.	Desk review of previous NICE submissions and then reference list scanning.	See Section 10.3.4

6. Efficacy

As described in Chapter 3.3.2, no approved active treatment is currently available in the ≥4L for advanced GIST patients in Denmark and thus no direct comparative treatment is applicable to this case. After treatment with imatinib, sunitinib and regorafenib, patients in Denmark receive BSC only (non-disease-specific agents to alleviate symptoms and facilitate patient comfort) ([redacted]). Therefore, to determine the cost-effectiveness of ripretinib in advanced GIST, the costs and benefits of adding ripretinib to the BSC versus no active treatment alongside BSC are considered. The INVICTUS study comparing ripretinib to placebo in GIST patients can be used for this direct comparison.

6.1 Efficacy of ripretinib compared to best supportive care for ≥4-line advanced GIST patients

6.1.1 Relevant studies

Ripretinib is indicated for the treatment of adult patients with advanced GIST previously treated with three TKIs, including imatinib. This population is in line with the patient population from the clinical trial that investigated the efficacy and safety of ripretinib: the INVICTUS trial (ClinicalTrials.gov 2022). Since no other comparative treatments are available for this patient population, the INVICTUS study is the only clinical trial used in this dossier to present the therapeutic value of ripretinib in advanced GIST. In this study, the ripretinib arm represents the addition of ripretinib to the treatment algorithm (i.e. imatinib, sunitinib, regorafenib, and then BSC) and the placebo arm represents BSC only in Danish clinical practice. The results of the INVICTUS study have been described in peer-reviewed publications (Blay et al. 2020, Bauer et al. 2021, Schöffski et al. 2022, Zalcberg et al. 2021) as well as presented at several conferences (von Mehren et al. 2019, von Mehren et al. 2021, Zalcberg et al. 2020, Becker et al. 2022, George et al. 2020, Serrano et al. 2020) (Table 10).

Table 10 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
Phase 3 Study of DCC-2618 vs Placebo in Advanced GIST Patients Who Have Been Treated With Prior Anticancer Therapies (INVICTUS) NCT03353753 DCC-2618-03-001 Peer-reviewed publications: (Blay et al. 2020, Bauer et al. 2021, Schöffski et al. 2022, Zalcberg et al. 2021)	Phase III, multinational, randomised double-blind, placebo-controlled clinical trial.	Primary endpoint: 27 months (2018-02-27 to 2019-05-31). Ripretinib: 6.3 months (IQR 3.2-8.2). Placebo: 1.6 months (IQR 1.1-2.7). Key data cut off: 15 January 2021. End of study: 11 May 2022.	129 patients (Ripretinib arm n=85, placebo n=) 44). Adults with advanced GIST after treatment or intolerance of at least three agents.	Oral ripretinib 150 mg once daily.	Placebo	**Progression-free survival** (Time Frame: From date of randomisation to the earliest date of disease progression or death from any cause [through database cut-off 31-May-2019 (up to approximately 15 months)), **Objective response rate** (Time Frame: From date of randomisation to the earliest date of disease progression or death from any cause [through database cut-off 31-May-2019 (up to approximately 15 months), **Time to Tumour Progression** based on Independent Radiologic Review [Time Frame: From date of randomisation to the earliest date of disease progression [through database cut-off 31-May-2019 (up to approximately 15 months)], **Overall Survival** [Time Frame: From the date of randomisation to the date of death from any cause [through database cut-off 31-May-2019 (up to approximately 15 months)], Quality of Life & Disease-Related Symptoms – **European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-Item – Role Functioning** [Time Frame: From the date of randomisation (Baseline) to Cycle 2 Day 1 (Month 2)], Quality of Life & Disease-Related Symptoms – **Physical Functioning [Time Frame: From the date of randomisation** (Baseline) to Cycle 2 Day 1 (Month 2)], Quality of Life & Disease-Related Symptoms – **EuroQol Visual Analogue Scale** [Time Frame: From the date of randomisation (Baseline) to Cycle 2 Day 1 (Month 2)].

Abbreviations: GIST: Gastrointestinal stromal tumour, NTC: National clinical trials.

6.1.1.1 INVICTUS (NCT03353753)

INVICTUS was a Phase III, two-arm, randomised, placebo-controlled, double-blind, international, multicentre study conducted at 29 specialised hospitals in 12 countries across North America, Europe and Asia to evaluate the safety and efficacy of ripretinib as 4L therapy (or further-line therapy) versus placebo in patients with advanced GIST (ClinicalTrials.gov 2022, Blay et al. 2020). The double-blinded period of the study was followed by an open-label period following disease progression. A graphical representation of the study design is shown in Figure 4 (Blay et al. 2020). Further details of the study characteristics are available in Appendix A.

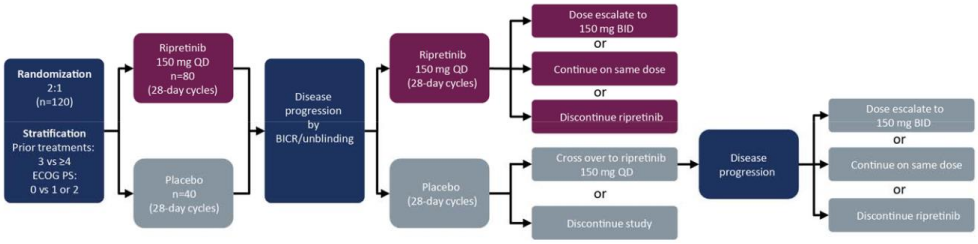


Figure 4 INVICTUS study design

Abbreviations: BICR: Blinded independent central review, BID: Bis in die, twice per day, ECOG PS: Eastern Cooperative Oncology Group performance score, QD: Quaque die, once daily.
Source: (Blay et al. 2020).

The main inclusion criteria of the INVICTUS study were (ClinicalTrials.gov 2022):

- Age ≥18 years
- Histological diagnosis of GIST
- Patients must have shown disease progression despite treatment with imatinib, sunitinib, and regorafenib or be intolerant despite dose modifications.
- Eastern Cooperative Oncology Group (ECOG) performance score of 0-2

Further previous treatments were permitted, provided it was ≥14 days or five times the drug's half-life before the first administration of the study drug (ClinicalTrials.gov 2022).

The main exclusion criteria were:

- Previous treatment with ripretinib
- A previous or concurrent malignancy whose natural course or treatment affects the safety or effectiveness of ripretinib.
- Patients with already known active metastases in the central nervous system.
- Severe cardiac disease (New York Heart Association class II-IV heart disease, active ischemia, or any other uncontrolled heart disease).
- Embolic events
- Any other clinically significant comorbidities

Eligible participants were randomly assigned (2:1) to either ripretinib (150 mg once daily) plus BSC or matching placebo tablets plus BSC for 28-day cycles. Patients, investigators, research staff, and the sponsor study team were masked to treatment allocation until the BICR confirmed progressive disease for the patient as defined by mRECIST version 1.1. At the time of BICR-confirmed progressive disease, patients were unblinded and those on placebo were offered the option to continue or crossover to ripretinib open-label. In addition, patients who progressed in the ripretinib arm were at investigator discretion able to continue at a higher dose (300 mg a day).

Tumour assessments using CT scans (Magnetic resonance imaging (MRI) scans were permitted for patients allergic to contrast media) were made at screening, then every cycle (28-days) through cycle four. After cycle four (or if once unblinded the patient was found to be on ripretinib), assessments were done every other cycle. If a patient crossed over from placebo to ripretinib, tumour assessments were done every other cycle, and again at the end of treatment. During the double-blind period, tumour assessments were performed based on BICR. An initial indication of a partial response or complete response based on the BICR was confirmed 4 or more weeks later. During the open-label period, overall response based on investigator assessments was used to guide treatment options.

In the INVICTUS study, 129 adult patients with advanced GIST were randomised 2:1 to ripretinib (n=85) or to placebo (n=44) (Blay et al. 2020) (intention-to-treat, ITT population). Of the randomised patients, 85 patients received at least one dose of ripretinib, and 43 patients received at least one dose of placebo treatment (Safety population). Patients in the ripretinib arm received 150 mg of ripretinib daily in the form of three oral tablets. Placebo and ripretinib were identical with respect to appearance and taste and thus were indistinguishable. The tablets could be taken with or without food. Both treatments were used until tumour progression, unacceptable toxicity, or study withdrawal. Treatment with ripretinib or placebo was added to the existing BSC regimen in both cases. During the open-label period, 68 patients received at least one dose of ripretinib, of which 42 patients switched from the placebo cohort and 26 patients were already in the ripretinib cohort.

The first patient was included on February 27, 2018. Efficacy and safety data are available from the primary analysis with cut-off date May 31, 2019. At the time of this analysis, median follow-up was 6.3 months (interquartile range (IQR) 3.2-8.2) for ripretinib patients and 1.6 months (IQR 1.1-2.7) for placebo patients (Blay et al. 2020). Follow-up analyses have been conducted: first with a cut-off date 10 August 2020 for EMA submission (EMA 2021a) as well as January 15, 2021, 19 months after the original data cut-off, for the current dossier (von Mehren et al. 2021). A graphical design of the patient flow at the cut-off date of January 15, 2021 is displayed in [redacted]. The end of study was in May 2022.

Figure 5

The efficacy analyses were conducted based on ITT principles. The primary endpoint of the INVICTUS study was PFS. The main secondary endpoints were ORR, OS, and HRQoL. To reduce the chance of a family-wise type 1 error, PFS, ORR, OS and HRQoL were hierarchically tested for statistical significance. These hypothesis tests for treatment differences were done sequentially in the following order: PFS, ORR, OS, and HRQoL as determined by changes from baseline to cycle two on day one in physical and role functioning scale subsets of the EORTC-QLQ-C30, with a two-sided 0.05 level of significance. Accordingly, if the outcome of any of the endpoints was not statistically significant (alpha of 0.05), the subsequent endpoints in the hierarchy could not be tested for statistical significance and were considered descriptive (Blay et al. 2020).

6.1.2 Comparability of studies

Not applicable, the comparison is based on the head-to-head study of INVICTUS (ripretinib + BSC vs. placebo + BSC).

6.1.2.1 Comparability of patients across studies

Baseline characteristics of the patients included in INVICTUS and accordingly in the comparative analysis of efficacy and safety underlying this application are presented in Table 11. The mean age of the patients was 60.1 years (standard deviation (SD): ±11.84) and slightly more men (57%) participated in the study than women (43%). Furthermore, most patients were white (75%), had had three previous treatments (63%), and slightly more than half had an ECOG status of 1 or 2 (56%) (Blay et al. 2020).

Table 11 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	INVICTUS	
	Ripretinib (n=85)	**Placebo (n=44)**
Age, median (range)	59 (29–82)	65 (33–83)
Sex		

Male, n(%)	47 (55%)	26 (59%)
Female, n(%)	38 (45%)	18 (41%)
Race		
White, n(%)	64 (75%)	33 (75%)
Non-white, n(%)	13 (15%)	7 (16%)
Not reported, n(%)	8 (9%)	4 (9%)
Region		
USA, n(%)	40 (47%)	20 (46%)
Non-USA, n(%)	45 (53%)	24 (55%)
N of previous therapies		
3, n(%)	54 (64%)	27 (61%)
4-7, n(%)	31 (36%)	17 (39%)
ECOG performance status		
0, n(%)	37 (44%)	17 (39%)
1 or 2, n(%)	48 (56%)	27 (61%)
Primary tumour site		
Gastric, n(%)	40 (47%)	18 (41%)
Jejunum or ileum, n(%)	20 (24%)	8 (18%)
Mesenteric or omental, n(%)	6 (7%)	6 (14%)
Other, n(%)	7 (8%)	4 (9%)
Duodenum, n(%)	2 (2%)	8 (18%)
Colon or rectum, n(%)	9 (11%)	0
Unknown, n(%)	1 (1%)	0
Sum of longest diameters of target lesions (mm)*, median (range)	123 (28-495)	142 (17-412)
Primary mutation		
KIT exon 19	14 (17%)	6 (14%)
KIT exon 11	47 (55%)	28 (64%)
Other KIT	2 (2%)	2 (5%)
PDGFRA	3 (4%)	0
KIT and PDGFRA wild type	7 (8%)	3 (7%)
Not available/not done†	12 (14%)	5 (11%)

*Independent assessment. †Tumour tissue analysed for baseline mutations, but analysis failed (not available) or Biopsy completed per protocol, but sample not received for analysis (not done).

Abbreviations: ECOG: Eastern Cooperative Oncology Group, KIT: KIT proto-oncogene, receptor tyrosine kinase, n: number, PDGFRA: Platelet-derived growth factor receptor A, USA: United States of America.

Source: (Blay et al. 2020).

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

The population entering the cost-effectiveness model are adult patients with advanced GISTs who have received prior treatment with ≥3 therapies including imatinib, in line with marketing authorisation and the ITT population of INVICTUS (Blay et al. 2020, EMA 2023b). [redacted] ([redacted]). The characteristics are summarised in Table 12.

Table 12 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (reference)	Value used in health economic model (reference if relevant)
Age	65 ([redacted])	60.1 (Blay et al. 2020)
Gender	60% male ([redacted])	56.6% male (Blay et al. 2020)
Patient weight	NA	NA

Abbreviations: NA: Not applicable.

6.1.4 Efficacy – results per study: INVICTUS NCT03353753

A summary of the PFS and OS results from INVICTUS which are utilised in the health economic model are presented below for the primary (May 31, 2019) and the later (January 15, 2021) data cut underlying the health economic model. The key secondary outcome objective response rate (ORR) is also summarised. Time-to-event data (PFS and OS) were summarised using the Kaplan-Meier (KM) method with two-sided 95% confidence intervals (CIs) (Blay et al. 2020). HRs were obtained from a Cox regression model in pre-specified analyses, and the 95% CIs with the Wald method. A summary of data checks follows the presented results. Further details are available in Appendix B.

Progression-free survival (PFS)

At the data cut off May 31, 2019, the primary endpoint of PFS as confirmed by BICR was met with a median PFS of 6.3 months (95% CI: 4.6 to 6.9) in the ripretinib arm versus 1.0 months (95% CI: 0.9 to 1.7) in the placebo arm (Blay et al. 2020). This represents a greater than 6-fold increase in PFS with ripretinib compared with placebo in a heavily pretreated, advanced patient population. The risk of disease progression or death (i.e., whichever came first) was 85% lower in the ripretinib arm than in the placebo arm and this was statistically significant (HR: 0.15, 95% CI: 0.09 to 0.25, p<0.0001). After 6 months, 51% (95% CI: 39.4% to 61.4%) of patients in the ripretinib arm were still alive progression-free versus 3.2% (95% CI: 0.2% to 13.8%) in the placebo arm. Furthermore, 51 (60%) patients in the ripretinib group experienced a PFS event and 34 (40%) were censored. In the placebo group, this corresponded to 37 (84%) and seven (16%), respectively.

In the follow-up data (data cut-off January 15, 2021) (von Mehren et al. 2021), PFS based on BICR remained stable in both treatment arms and median PFS was similar to that reported in the primary analysis (median PFS 6.3 months [95% CI: 4.6 to 8.1] versus 1.0 [95% CI: 0.9 to 1.7]) (See Figure 6). Accordingly, the direct comparison of ripretinib versus placebo shows that the probability that a patient is progression-free at any time is statistically significantly greater for patients treated with ripretinib than for placebo patients, with a HR of 0.16. It can be concluded that the effect of ripretinib versus placebo on PFS is also clinically relevant ([redacted]).

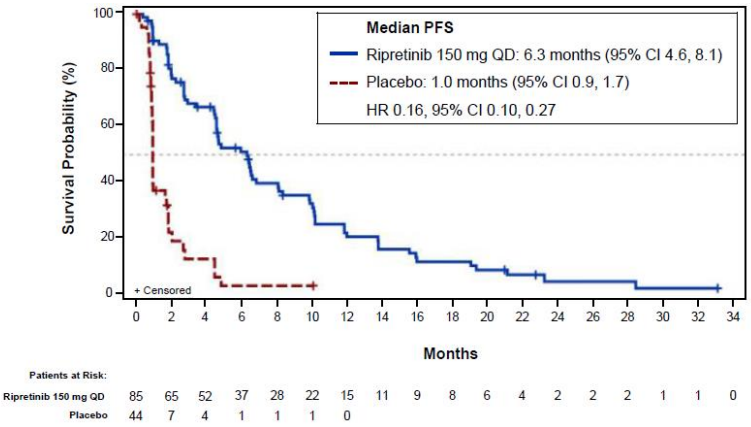


Figure 6 Kaplan-Meier PFS follow-up analysis (ITT population + crossover, data cut 15 January 2021)

Abbreviations: CI: Confidence interval, ITT: Intention to treat, OS: Overall survival, QD: Quaque die, once daily.
Source: (von Mehren et al. 2021).

Overall survival (OS)

Given the hierarchical statistical testing procedure of the endpoints, OS was tested only descriptively because the difference in ORR, which was determined after PFS, was not statistically significant despite showing clinically relevant differences (Blay et al. 2020).

At the primary analysis data cut-off, 26 (31%) patients in the ripretinib group experienced an OS event and 59 (69%) were censored. In the placebo group, this corresponded to 26 (59%) and 18 (41%), respectively (Blay et al. 2020). The median OS of the ripretinib patients was 15.1 months (95% CI: 12.3 to 15.1) versus 6.6 months (95% CI: 4.1 to 11.6) in the placebo group with the difference leading to an HR of 0.36 (95% CI: 0.21 to 0.62). Although the statistical significance of this could not be tested, the data suggests that ripretinib reduced the risk of death by 64% compared with placebo.

There is mature OS data for ripretinib. The follow-up analysis (data cut-off January 15, 2021) showed improved median OS for ripretinib patients compared with the primary analysis (18.2 months, 95% CI: 13.1 to 30.7) (See Figure 7) (von Mehren et al. 2021). The median OS of the placebo group was slightly lower than in the primary analysis (6.3, 95% CI: 4.1 to 10.0). The HR was 0.41 (95% CI: 0.26 to 0.65). In addition, the median OS for the placebo crossover patients was higher than that of the placebo group but lower than that of the randomised ripretinib group at 10.0 months (95% CI: 6.3 to 20.9).

As per the study design for INVICTUS, study drug treatment was unblinded upon disease progression and patients randomly assigned to placebo were given the option to crossover to receive open-label ripretinib. Hence the true survival associated with placebo could be confounded with the treatment benefits of crossover onto open-label ripretinib among those originally randomised to placebo, resulting in the conventional analyses presented above underestimating the survival benefit associated with treatment with ripretinib. Due to the high proportion of patients who crossed over (30/44 patients; 68%), utilising the

results of the ITT analysis for OS in the health economic model within this application was deemed inappropriate as the majority of patients in the placebo arm of the trial received ripretinib. The model used to adjust for cross-over was the standard two-stage cross-over adjustment model (see section D.1.9).

Thus, the direct comparison of ripening versus placebo in INVICTUS suggests that the likelihood of a patient being alive at any time is greater for patients treated with ripretinib than placebo. Although the difference was not tested for statistical significance owing to the hierarchical testing plan, these data show the clinically significant benefit of ripretinib in survival. The reduced median OS observed in the placebo arm reflects the aggressive nature of advanced GISTs. The possible crossover of patients randomised to placebo to ripretinib treatment upon disease progression is relevant for the interpretation of these estimates and likely leads to an underestimation of the treatment effect in the ITT analyses. Notably, patients in the placebo crossover group appear to have a survival advantage over those remaining on placebo. As displayed in Figure 7, median OS in the cross group was 10 months compared to 6.3 months in the placebo group. The fact that median OS in the crossover group remained lower than that of the randomised ripretinib group implies that timely initiation of ripretinib promotes OS.

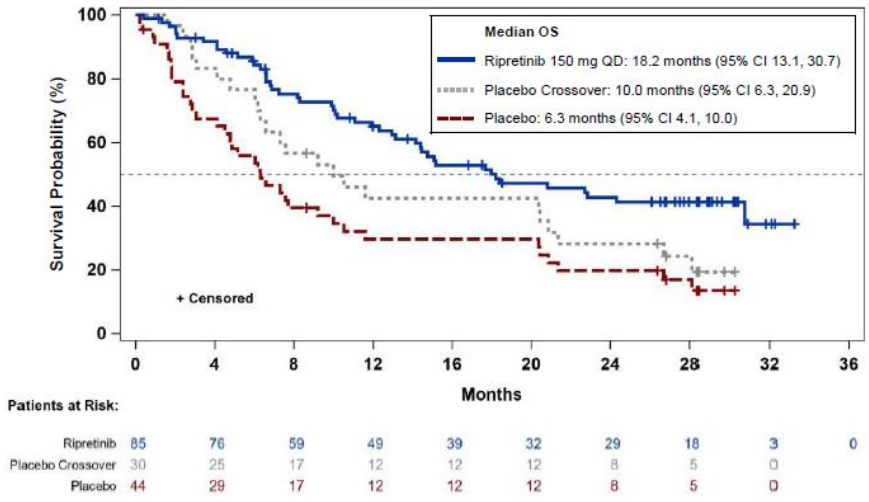


Figure 7 Kaplan-Meier OS curve follow-up analysis (ITT population + crossover, data cut 15 January 2021)

Abbreviations: CI: Confidence interval, ITT: Intention to treat, OS: Overall survival, QD: Quaque die, once daily.
Source: (von Mehren et al. 2021).

Objective response rate (ORR)

Maintaining stable disease is a valuable endpoint in GIST. In the ripretinib group, 9% (95% CI: 4% to 18%) of patients had a confirmed objective response, all of which were partial responses confirmed by BICR, versus 0% (95% CI: 0% to 8%) in the placebo group (Blay et

al. 2020). The difference in ORR between the two treatment arms just missed statistical significance (p=0.0504) and owing to this, no further endpoints, including OS, were tested for statistical significance. At the later data cut, January 15 2021, 11.8% of ripretinib randomised patients and 0% of placebo patients had a confirmed objective response, [redacted] ([redacted]). The direct comparison of ripretinib and placebo suggests a trend towards improvement in ORR with treatment with ripretinib and thus disease stability.

Data checks for PFS and OS

The proportional hazards (PH) assumption was checked to ascertain the appropriateness of the pre-specified survival analyses for both PFS and OS for the primary data cut (Blay et al. 2020, [redacted]), as well as for the data cut January 15, 2021 underlying the present application ([redacted]). The latter is presented here. Two statistical tests were conducted: the complementary log-log plot and the Schoenfeld residuals test.

[redacted] ([redacted]).

[redacted]

Figure 8

[redacted]

Abbreviations: ITT: Intention to treat, PFS: Progression-free survival, QD: Quaque die, once daily.
Source: ([redacted]).

[redacted].

[redacted]

Figure 9

[redacted]

Abbreviations: ITT: Intention to treat, OS: Overall survival, QD: Quaque die, once daily.
Source: ([redacted]).

[redacted]

Efficacy conclusions

The direct comparison of ripretinib versus placebo in INVICTUS shows that the probability that a patient is progression-free at any time is greater for patients treated with ripretinib than for placebo patients (Blay et al. 2020). Maintaining stable disease is a valuable endpoint in advanced GIST. The direct comparison of ripretinib and placebo also suggests a trend toward improvement in ORR. Since ORR, the key secondary endpoint, did not reach significance at a 0.05 significance level, and due to the hierarchical alfa spending strategy, the OS results are not type-1 error controlled, however the OS data indicates a prolonged survival for advanced GIST patients treated with ripretinib compared with placebo (Mehren et al. 2021). Consistent results were also demonstrated for the relevant subgroups analysed, i.e. by age, gender, race, region, baseline ECOG status and number of prior systemic anticancer therapies (EMA 2021a). Updated efficacy data, demonstrated continued efficacy and robustness of results with ripretinib for patients with advanced GIST compared with placebo with regard to key efficacy results for the double-blind period and crossover patients in the open-label period (EMA 2021a, Mehren et al. 2021).

7. Comparative analyses of efficacy

Not applicable as INVICTUS was a randomised controlled study comparing the intervention (ripretinib + BSC) with the comparator (placebo + BSC) directly.

7.1.1 Differences in definitions of outcomes between studies

7.1.2 Method of synthesis

7.1.3 Results from the comparative analysis

Table 13 Results from the comparative analysis

Outcome measure	Intervention (n=)	Comparator (n=)	Result

7.1.4 Efficacy – results per [outcome measure]

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

8.1.1 Extrapolation of efficacy data

Clinical effectiveness parameters are based on data from the INVICTUS study. Survival analysis extrapolation was required to inform state transitions in the model, allowing for evaluation of clinical outcomes over a longer time horizon than that observed in the trial. At the data cut-off of 31 May 2019, the median follow-up time in the double-blind period was 6.3 months (IQR 3.2 to 8.2) for the ripretinib group and 1.6 months (1.1 to 2.7) for the placebo group (Blay et al. 2020). Disease progression or death (PFS event) occurred in 60% of patients in the ripretinib group (34 [40%] of patients were censored) and in 84% in the placebo group (seven [16%] patients were censored) (Blay et al. 2020). From mature OS data for the most recent data cut-off (15 January 2021), 46 (54%) patients in the ripretinib group experienced an OS event (39 [46%] were censored) and 36 (82%) patients in the placebo group experienced an OS event (8 [18%] were censored) (von Mehren et al. 2021).

8.1.1.1 Extrapolation of overall survival

Table 14 presents a summary of assumptions associated with extrapolation of OS.

Table 14 Summary of assumptions associated with extrapolation of overall survival

Method/approach	Description/assumption
Data input	INVICTUS

Model	Full parametrization of standard parametric models
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	Ripretinib: [redacted] function BSC: [redacted] function
Function with best BIC fit	Ripretinib: [redacted] function BSC: [redacted] function
Function with best visual fit	Ripretinib: [redacted] function BSC: [redacted] function
Function with best fit according to evaluation of smoothed hazard assumptions	-
Validation of selected extrapolated curves (external evidence)	-
Function with the best fit according to external evidence	-
Selected parametric function in base case analysis	Ripretinib: [redacted] function BSC: [redacted] function
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	OS for BSC adjusted for cross-over using two-stage model approach (Latimer NR 2014).
Assumptions of waning effect	No
Assumptions of cure point	No

Abbreviations: AIC: Aikaike information criterion, BIC: Bayesian information criterion.

Appendix D.1 presents detailed information motivating the most suitable model for adjusting for treatment cross-over, along with standard tests and figures motivating the selection of most credible statistical model to extrapolate OS.

The model predicted survival times, adjusted background mortality estimated based on life tables published by the Danish Medicines Council (Danish Medicines Council 2024), are displayed in [redacted]. The [redacted] distribution was selected to inform parametric

function in base case analysis for both ripretinib and BSC.

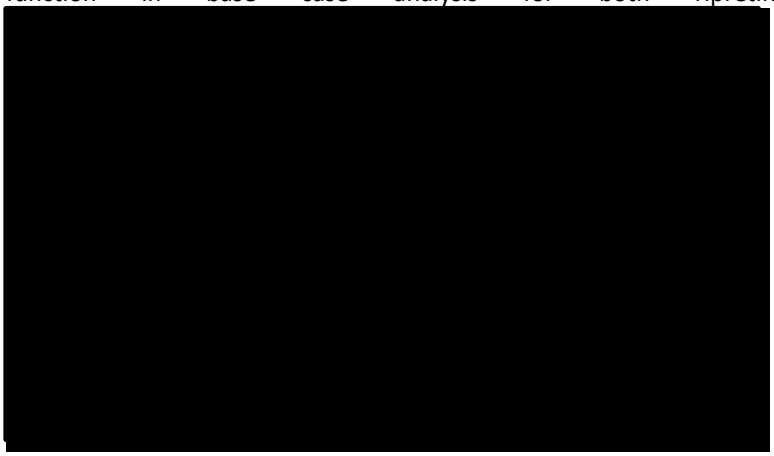


Figure 10:

Abbreviations: BSC: Best supportive care, KM: Kaplan-Meier.

8.1.1.2 Extrapolation of progression-free survival

Table 15 presents a summary of assumptions for the extrapolation of PFS for ripretinib.

Table 15 Summary of assumptions associated with extrapolation of progression-free survival for ripretinib

Method/approach	Description/assumption
Data input	INVICTUS
Model	Full parametrization of standard parametric models
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	Ripretinib: function BSC: function
Function with best BIC fit	Ripretinib: function BSC: function
Function with best visual fit	Ripretinib: function BSC: function
Function with best fit according to evaluation of smoothed hazard assumptions	-

Method/approach	Description/assumption
Validation of selected extrapolated curves (external evidence)	-
Function with the best fit according to external evidence	-
Selected parametric function in base case analysis	Ripretinib: [redacted] function BSC: [redacted] function
Adjustment of background mortality with data from Statistics Denmark	Not applicable
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

Abbreviations: AIC: Akaike information criterion, BIC: Bayesian information criterion, BSC: Best supportive care.

Appendix D.2 presents detailed information, standard tests and figures, motivating the selection of statistical model to extrapolate PFS. Six standard parametric independent models were fitted to each arm of the study data; exponential, Weibull, Gompertz, log-logistic, log-normal and the generalised gamma ([redacted]).

Given the maturity of the progression free survival endpoint (77.6% and 84.1% progression for ripretinib and placebo, respectively), the independent parametric curves all fitted the data and produced good visual predictions for ripretinib and BSC within the observed period. The [redacted] distribution was selected to inform parametric function in base case analysis for both ripretinib and BSC.

[redacted]

Figure 11: [redacted]

Abbreviations: BSC: Best supportive care, KM: Kaplan-Meier, PFS: Progression-free survival.

8.1.1.3 Extrapolation of time to discontinuation for ripretinib

Table 16 presents a summary of assumptions associated with extrapolation of time to discontinuation for ripretinib.

Table 16 Summary of assumptions associated with extrapolation of time to discontinuation for ripretinib

Method/approach	Description/assumption
Data input	INVICTUS
Model	Full parametrization of standard parametric models
Assumption of proportional hazards between intervention and comparator	Not applicable
Function with best AIC fit	Ripretinib: [redacted] function BSC: Not applicable
Function with best BIC fit	Ripretinib: [redacted] function BSC: Not applicable
Function with best visual fit	Ripretinib: [redacted] function BSC: Not applicable
Function with best fit according to evaluation of smoothed hazard assumptions	Not applicable
Validation of selected extrapolated curves (external evidence)	-
Function with the best fit according to external evidence	-
Selected parametric function in base case analysis	Ripretinib: [redacted] function BSC: Not applicable
Adjustment of background mortality with data from Statistics Denmark	Not applicable
Adjustment for treatment switching/cross-over	Not applicable
Assumptions of waning effect	Not applicable
Assumptions of cure point	Not applicable

Abbreviations: AIC: Akaike information criterion, BIC: Bayesian information criterion, BSC: Best supportive care.

Patients in the ripretinib arm of the INVICTUS trial were offered to continue ripretinib treatment following progression in the open-label phase. While the continued effect of treatment beyond progression is unclear, input from clinicians suggested that, in the case of 4L therapy where no further treatment options are available, ripretinib treatment may be continued. This phenomenon was therefore captured in the ripretinib arm of the model through the division of the PD state into two substates: on treatment and off treatment.

Appendix D.3 presents information motivating the selection of statistical model to extrapolate the composite endpoint. [redacted] presents seven standard parametric independent models fitted to the study data: exponential, Weibull, Gompertz, log-logistic, log-normal, gamma, and generalised gamma. The [redacted] model was selected as the default on the basis that it had the lowest AIC and BIC of the eight models.

Figure 12: [redacted]

Abbreviations: AIC: Akaike information criterion, BIC: Bayesian information criterion, LL; lower limits.

8.1.2 Calculation of transition probabilities

Not applicable, Table 17 is therefore left blank.

Table 17 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
Disease-free survival	Recurrence		
	Death		
Recurrence	Death		
Health state/Transition		Not applicable	

8.2 Presentation of efficacy data from [additional documentation]

Not applicable.

8.3 Modelling effects of subsequent treatments

Since there are no other approved treatments recommended in the ≥4L of treatment, no subsequent treatments are included in the model.

8.4 Other assumptions regarding efficacy in the model

Not applicable.

8.5 Overview of modelled average treatment length and time in model health state

Table 18 presents mean and median OS and PSF for ripretinib and BSC, along with the observed statistics from INVICTUS.

Table 18 Estimates in the model

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
Ripretinib	Mean PFS: 9.82 months Mean OS: 45.76 months (Sheet 'Partitioned Survival Model')	Median 5.54 months Median OS: 20.31 months (Sheet 'Partitioned Survival Model')	Median PFS: 6.36 months Median OS: 18.26 months (INVICTUS, unadjusted KM-data, sheet 'KM Data')
BSC	Mean PFS: 2.17 months Mean OS: 4.94 months (Sheet 'Partitioned Survival Model')	Median PFS: 1.85 Median OS: 3.69 (Sheet 'Partitioned Survival Model')	Median PFS: 0.96 months Median OS: 1.58 months (INVICTUS, unadjusted KM-data, sheet 'KM Data')

Abbreviations: BSC: Best supportive care, KM: Kaplan-Meier, OS: Overall survival, PFS: Progression free survival.

Table 19 shows the modelled average treatment length and time in model health state of PFS, PD on treatment (PD(t)) and PD off treatment (PD). Treatment length is calculated as the summation of the time spend in the PFS and the PD on treatment health state.

Table 19 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction

Treatment	Treatment length [months]	Health state PFS [months]	Health state PD(t) [months]	Health state PD [months]
Ripretinib	17.62	9.82	7.80	28.18
BSC	-	2.17	-	2,77

Abbreviations: BSC: Best supportive care, PD: Progressed disease, PFS: Progression free survival.

9. Safety

The documentation of the safety of ripretinib is based on the pivotal trial INVICTUS.

9.1 Safety data from the clinical documentation

The safety profile of ripretinib was deemed acceptable based on the INVICTUS study (EMA 2021a, Blay et al. 2020). Adverse events (AEs) that occurred during treatment with a study drug (TEAE, treatment-emergent adverse events) were as expected and indicate a favourable safety profile of ripretinib (Blay et al. 2020). Treatment-related TEAEs (or adverse reactions) are also reported. Unless otherwise specified, the data presented relates to the primary data cut-off (31 May 2019). Mature INVICTUS safety data after an additional 19 months was consistent with the primary analysis (von Mehren et al. 2021). The data for ripretinib was considered sufficiently comprehensive to characterise the safety profile given the rarity of the disease and the later line indication (EMA 2021a).

Safety population data

The safety population was defined as all patients who received at least one dose of study drug. The safety population for the blinded period of the study (data cut-off May 31, 2019) comprised 85 ripretinib and 43 placebo randomised patients who also received a study drug (Blay et al. 2020). While 44 patients were randomised to placebo, one patient did not receive a study drug and is not included in the safety population.

Treatment exposure

In the double-blind period, the mean treatment duration for the ripretinib arm ([redacted]) was longer than that of the placebo arm ([redacted]) for the ripretinib and placebo arms respectively ([redacted]).

Among ripretinib patients, five (6%) of 85 patients had a treatment-related TEAE leading to a dose reduction, and this was found for one (2%) of 43 patients who received placebo (Blay et al. 2020). In the ripretinib arm, 12 (14.1%) had had a treatment-related TEAE leading to any dose interruption, and 4 (4.7%) leading to study treatment discontinuation (due to cardiac failure, death of unknown cause, general physical health deterioration, and palmar–plantar erythrodysesthesia also known as hand-foot syndrome) (Blay et al. 2020).

In the placebo arm, 3 (7.0%) had a treatment-related TEAE leading to any dose interruption and had a treatment-related TEAE lead to 1 (2.3%) discontinuing study treatment (due to fatigue) (Blay et al. 2020). Dose increases occurred when returning to the prior dose. The median relative dose intensity (RDI) was 100% (IQR 98.1–100.0) for the ripretinib group and 97% (86.5–100.0) for the placebo group (Blay et al. 2020). Regarding deaths, twelve (14%) of 85 patients in the ripretinib group died (11 deaths due to disease progression and one death due to an unknown reason) and 13 (30%) of 43 patients in the placebo group died (eleven deaths due to disease progression and two deaths due to an AE [one acute kidney injury and one septic shock]) (Blay et al. 2020). Treatment-related TEAEs leading to death were rare, and only reported by one patient in each of the ripretinib (1.2%) and placebo (2.3%) arms (Blay et al. 2020).

Overview of safety events

At the primary data analysis data-cut and point of unblinding (May 31, 2019), [redacted] ([redacted]). Table 20 below contains an overview of safety events and treatment exposure from the INVICTUS trial.

Table 20 Overview of safety events (INVICTUS double-blind period, data-cut 31 May 2019)

	Ripretinib (n=85) (INVICTUS)	Placebo (n=43) (INVICTUS)	Difference, % (95 % CI)
Number of adverse events, n	[redacted]	[redacted]	[redacted]
Number and proportion of patients with ≥1 adverse events, n (%)	[redacted]	[redacted]	[redacted]
Number of serious adverse events*, n	[redacted]	[redacted]	[redacted]
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	[redacted]	[redacted]	[redacted]
Number of CTCAE grade ≥ 3 events, n	[redacted]	[redacted]	[redacted]
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	42 (49.4)	19 (44.2)	[redacted]
Number of adverse reactions, n	[redacted]	[redacted]	[redacted]
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	[redacted]	[redacted]	[redacted]
Number and proportion of patients who had a dose reduction, n (%)	7 (8.2)	1 (2.3)	[redacted]

Number and proportion of patients who discontinue treatment regardless of reason, n (%)	17 (20.0)	13 (30.2)	[redacted]
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	4 (4.7)	1 (2.3)	[redacted]

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

§ CTCAE v. 5.0 must be used if available.

Abbreviations: CI: Confidence interval, CTCAE: Common terminology criteria for adverse events, n: number, NR: Not reported.

Source: (Blay et al. 2020) [redacted].

During the double-blind treatment period both treatment arms were comparable regarding any TEAE (Blay et al. 2020). The most frequent (occurring in ≥20% of patients in the ripretinib group) treatment-related TEAEs in patients receiving ripretinib were alopecia (42, 49.4%), myalgia (24 [28.2%]), nausea and fatigue (22 [25.9%] patients each), and diarrhoea and palmar-plantar dysesthesia syndrome (18 [21.2%] patients each) (Blay et al. 2020). Palmar-plantar erythrodysesthesia occurred exclusively in patients treated with ripretinib and all events were grade 1 or 2 (Blay et al. 2020). The most frequent (>2%) grade ≥3 treatment-related TEAEs in the ripretinib group were lipase increase (four [5%] of 85 patients), hypertension (three [4%]), fatigue (two [2%]), and hypophosphatemia (two (2%]) (Blay et al. 2020). The corresponding for the placebo arm were anaemia (three [7%] of 43 patients), fatigue (one [2%]), diarrhoea (one [2%]), decreased appetite (one [2%]), dehydration (one [2%]), hyperkalaemia (one [2%]), acute kidney injury (one [2%]), and pulmonary oedema (one [2%]) (Blay et al. 2020).

[redacted] ([redacted]). Further details on the serious AEs are in Table 21 and Appendix E.

Table 21 Serious treatment-emergent adverse events in either study arm having ≥2% of patients with an adverse event (INVICTUS double-blind period, data-cut May 31, 2019)

Adverse events	Intervention Ripretinib (N=85)		Comparator Placebo (N=43**)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

**44 patients were assigned placebo, but one patient did not receive treatment.

*** Treatment-emergent AEs are defined as any AE that occurs after administration of the first dose of the study drug and through 30 days after the last dose of the study drug.

Abbreviations: n: number, NR: Not reported, TEAE: Treatment-emergent adverse event.

Source: [redacted]

Long term safety data

Furthermore, the safety profile of ripretinib from the primary analyses has been confirmed by updated safety analyses (EMA 2021a, von Mehren et al. 2021). No new safety concerns were identified with longer exposure to ripretinib, nor did the tolerability profile change significantly (EMA 2021a, von Mehren et al. 2021). By January 15, 2021, the median blinded treatment duration [redacted]. The most frequent of which were abdominal pain, anaemia, and hypertension which occurred in >5% in at least one arm (von Mehren et al. 2021).

Ripretinib's safety profile by age, gender, race, geographic region, body mass index, and line of therapy was also provided in EMA approval process, with this data not evoking any concerns (EMA 2021a). Nor has any US post-marketing data shown any new or worrisome signals in the six-month period 15 May 2020 to 31 December 2020 (EMA 2021a).

Safety profile conclusions

The reported rates of TEAEs, Grade 3/4 events and SAEs are recognised. Nonetheless, as a ≥4L treatment, the safety profile of ripretinib was deemed acceptable and the initial safety profile of ripretinib was confirmed in later safety analyses (EMA 2021a).

Ripretinib also holds a favourable safety profile compared with other agents that comprise treatment for advanced GIST (imatinib, sunitinib and regorafenib) based on the information in the respective summary of product characteristics (EMA 2023b, EMA 2023d, EMA 2021b, EMA 2023a). Many of the side effects that were reported for these agents were either occasional or infrequent with ripretinib (EMA 2023b, EMA 2023d, EMA 2021b, EMA 2023a). Although the use of all four agents is associated with the occurrence of AEs, ripretinib and imatinib appear to have more favourable safety profiles than sunitinib and regorafenib. The EMA recognised that there is overall a high report rate of TEAEs, including grade 3 or 4 events and SAEs. Reassuringly however, there was a low rate of treatment discontinuations and a low rate of patients that needed a dose reduction due to AEs in INVICTUS. Taken together, EMA concluded that ripretinib has a favourable safety profile with manageable toxicity (EMA 2021a).

Use of safety data in the health economic model

TEAEs (severity grade ≥3) occurring in ≥5% of patients in either treatment arm of INVICTUS at the data cut-off 15 January 2021 were included in the health economic model (Table 22) (von Mehren et al. 2021).

Table 22 Adverse events used in the health economic model

Adverse events	Intervention Ripretinib (N=85)	Comparator Placebo (N=43*)		
	Frequency used in economic model for intervention	**Frequency used in economic model for comparator**	**Source**	**Justification**
Anaemia	9 (10.6%)	6 (14.0%)	(von Mehren et al. 2021)	Included TEAEs correspond to a severity grade 3/4 and were the most frequently reported in INVICTUS
Abdominal pain	6 (7.1%)	2 (4.7%)		
Hypertension	6 (7.1%)	0		

* 44 patients were randomised to placebo but one did not receive study treatment

Abbreviations: n: number, TEAE: Treatment-emergent adverse event.

9.2 Safety data from external literature applied in the health economic model

Not applicable. Adverse events included in the health economic model were all taken from the INVICTUS trial and hence Table 23 is left blank.

Table 23 Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n								

10. Documentation of health-related quality of life (HRQoL)

Quality of life (QoL) was measured in the INVICTUS clinical trial using the EQ-5D-5L and the EORTC QLQ-C30 questionnaires ([redacted], ClinicalTrials.gov 2022, Schöffski et al. 2022). Accordingly, two different PROs were collected in the INVICTUS study (Table 24):

- EQ-5D: EQ-5D-5L questionnaire consisting both of five dimensions resulting in the index score and the Visual Analogue Scale (VAS)
- European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-item (EORTC QLQ-C30)

The results of the EQ-5D-5L index score were used to derive the utilities for the cost-effectiveness model. The other patient-reported outcomes in INVICTUS were not included in the cost-effectiveness model in this application, for further details please see Appendix F. Focus below is on the EQ-5D from INVICTUS as it is directly applied into this application. In addition, EQ-5D data from GRID was utilised in this application (Poole et al. 2015).

Table 24 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	INVICTUS	Assessed global HRQoL. Consists of two items: EQ-5D descriptive system (measures mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and the EQ-VAS (measures the patient's self-rated health on a vertical visual analogue scale) (EuroQoL 2024). The five-domain descriptive system was used to calculate the utility score with Danish weights for this submission
EORTC QLQ-C30	INVICTUS	Assessed disease-related symptoms. Cancer-specific QoL questionnaire designed to measure cancer patients' physical, psychological, and social functions. (Kaasa et al. 1995, EORTC Quality of Life 2024)

10.1 Presentation of the health-related quality of life

Below follows the HRQoL data from INVICTUS using the EQ-5D-5L instrument that was included in the health economic model of this application. Given the generic nature of the EQ-5D instrument, INVICTUS also included the disease-specific instrument to capture specific domains that are particularly relevant for patients with cancer (See Appendix F.2).

10.1.1 Study design and measuring instrument

The ITT population contributing to HRQoL data in INVICTUS was the same as that for clinical efficacy, see Section 6.1.1.1 for details. Of note for the HRQoL data is that it was permitted for patients to continue treatment post progression.

The EQ-5D is a validated, standardised questionnaire developed by the EuroQoL Group which is completed by patients to measure their overall health status. It is commonly used in clinical studies to provide a measure of patient utility for clinical and economic appraisals as it is a generic instrument used across various disease areas (EuroQol Research Foundation 2021). Within INVICTUS, validated translations of the EQ-5D-5L were provided for sites in non-English-speaking countries. The EQ-5D-5L represented a revision to the original EQ-5D-3L (with 3 response levels per item) and had been shown to significantly increase reliability and sensitivity (discriminatory power) while maintaining ease of completion. The Danish utility weights have been applied for this application.

The first five items measure the health dimensions of mobility, ability to conduct self-care, ability to conduct usual activities, pain/discomfort, and anxiety/depression. The patient selected from 5 response levels (no problems, slight problems, moderate problems, severe problems, extreme problems) to rate their level of difficulty on that dimension that day. The sixth item was a visual analogue scale (VAS). The EQ-VAS measures patient self-reported health on a vertical visual scale with endpoints labelled “worst imaginable health status” at 0 and “best imaginable health status” at 100. The patient is asked to mark their perceived health status on the scale as they feel “today” as well as write the number marked. This information can be used as a quantitative measure of health status as judged by the individual patient. On the EQ-5D VAS, an increase in the score means an improvement, while a decrease in the score means a deterioration in health status. The minimal clinically important difference (MCID) ranges from 7–8 points for anchor-based estimates and 9–11 points for distribution-based estimates from a retrospective analysis of patients with various types of cancers (Pickard et al. 2007).

There were a priori expectations were of stable HRQoL while experiencing stable disease and with decrements associated with disease progression. Such decrements in HRQoL are commonly observed in clinical practice in conjunction with disease progression ([redacted]). Hence, it was expected that patients in the ripretinib arm may maintain their HRQoL to a greater extent over time than those patients in the placebo arm.

10.1.2 Data collection

During treatment, patient-reported HRQoL instruments were completed electronically before dosing on days 1 (baseline) and 15 of cycle 1, day 1 of subsequent cycles, and within 7 days of the last dose (end-of-treatment visit) (Schöffski et al. 2022). [redacted] ([redacted]). [redacted] ([redacted]).

A report of the relevant data collection time points and pattern of missing data of the EQ-5D instrument from the May 2022 data cut is presented in Table 25.

Table 25 Pattern of missing data and completion for EQ-5D during the double-blind period [INVICTUS ITT population, May 2022 data cut]

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Total number of patients (ripretinib + placebo)	Number of patients for whom data is missing (% of patients at randomisation)	Number of patients "at risk" at time point	Number of patients who completed (% of patients expected to complete)
Cycle 1, Day 1 (baseline)	129	0 (0%)	129	116 (89.9%)
Cycle 2, Day 1	129	7 (5.4%)	122	111 (91.0%)
Cycle 3, Day 1	129	35 (27.1%)	94	82 (87.2%)
Cycle 4, Day 1	129	52 (40.3%)	77	70 (90.9%)
Cycle 5, Day 1	129	61 (47.3%)	68	58 (85.3%)
Cycle 6, Day 1	129	69 (53.5%)	60	51 (85.0%)
Cycle 7, Day 1	129	81 (62.8%)	48	40 (83.3%)
Cycle 8, Day 1	129	84 (65.1%)	45	40 (88.9%)
Cycle 9, Day 1	129	93 (72.1%)	36	30 (83.3%)
Cycle 10, Day 1	129	96 (74.4%)	33	31 (93.9%)

Abbreviations: HRQoL: Health.-related quality of life, N: Number.
Source: (The Federal Joint Committee (G-BA) 2019)

No missing data were imputed (Schöffski et al. 2022). The declining number of patients with PRO data over time reflects the number who remained progression-free. The number of patients in the placebo arm declined quickly due to disease progression, making intergroup comparisons beyond cycle 2 difficult (Schöffski et al. 2022).

10.1.3 HRQoL results

EQ-5D index

EQ-5D-5L from the May 31 2019 data cut was summarised for each level of each dimension ([redacted], EMA 2021a). See Appendix F.1. for the dimensions of relevance to advanced GIST patients, pain/discomfort and usual activities.

For EQ-5D-5L index (utility) score with Danish utility weights (Jensen et al. 2021), a mixed model for repeated measures (MMRM) was used to calculate adjusted mean changes from baseline and to compare changes from baseline between treatment arms using data from the January 15, 2021 data cut ([redacted]). A summary is provided in Table 26. Mean (SD) baseline utility score was [redacted] and [redacted] for the ripretinib and placebo arms, respectively. The adjusted mean (SD) change from baseline to C2D1 in utility score was [redacted] and [redacted] for the ripretinib and the placebo arms, respectively with a difference between the arms of [redacted].

Table 26 HRQoL EQ-5D-5L index score summary statistics [INVICTUS ITT population, January 15, 2021 data cut]

	Ripretinib 150 mg (N=85)			Placebo (N=44)			Ripretinib vs Placebo
	n	Number expected to complete	Mean (SE)	n	Number expected to complete	Mean (SE)	Difference (95% CI) p-value
Baseline	[redacted]						
Cycle 1 Day 15	[redacted]						
CFB to Cycle 1 Day 15 (Observed)	[redacted]						
CFB to Cycle 1 Day 15 (MRMM)	[redacted]						
Cycle 2 Day 1	[redacted]						
CFB to Cycle 2 Day 1 (Observed)	[redacted]						
CFB to Cycle 2 Day 1 (MMRM)	[redacted]						

	Ripretinib 150 mg (N=85)	Placebo (N=44)	Ripretinib vs Placebo
Cycle 3 Day 1	[redacted]	[redacted]	
CFB to Cycle 3 Day 1 (Observed)	[redacted]	[redacted]	
CFB to Cycle 3 Day 1 (MMRM)	[redacted]	[redacted]	[redacted]
Cycle 4 Day 1	[redacted]	[redacted]	
CFB to Cycle 4 Day 1 (Observed)	[redacted]	[redacted]	
CFB to Cycle 4 Day 1 (MMRM)	[redacted]	[redacted]	[redacted]
Cycle 5 Day 1	[redacted]	[redacted]	
CFB to Cycle 5 Day 1 (Observed)	[redacted]	[redacted]	
Cycle 6 Day 1	[redacted]	[redacted]	
CFB to Cycle 6 Day 1 (Observed)	[redacted]	[redacted]	
Cycle 7 Day 1	[redacted]	[redacted]	
CFB to Cycle 7 Day 1 (Observed)	[redacted]	[redacted]	

	Ripretinib 150 mg (N=85)	Placebo (N=44)	Ripretinib vs Placebo
Cycle 8 Day 1	[redacted]	[redacted]	
CFB to Cycle 8 Day 1 (Observed)	[redacted]	[redacted]	
Cycle 9 Day 1	[redacted]	[redacted]	
CFB to Cycle 9 Day 1 (Observed)	[redacted]	[redacted]	
Cycle 10 Day 1	[redacted]	[redacted]	
CFB to Cycle 10 Day 1 (Observed)	[redacted]	[redacted]	

For change in EQ-5D-5L Index Utility Score, the LS mean, SE, 95% CI, and diiference in LS mean and p-value are estimated from an MMRM model that includes factors for study treatment, visit, treatment by visit interaction, number of prior anticancer treatments, ECOG performance status at baseline and EQ-5D-5L utility score at baseline as fixed effects. Treatment difference is placebo – ripretinib. Note the DK preference weights have been utilised. Owing to few patients in placebo arm, only observed values are presented from Cycle 3. n= number of questionnaires completed.
Abbreviations: CFB: Change from baseline, CI: Confidence interval; ECOG: Eastern Cooperative Oncology Group, LS: Least squares; MRMM: Mixed model for repeated measures, NR: Not reported; SD: Standard deviation; SE: Standard error.
Source: [redacted] ([redacted])

The observed EQ-5D-5L index scores of patients in the ripretinib group remained stable over time as visualised in [redacted].

Figure 13:

Abbreviations:CI: Confidence interval, EQ-5D: EuroQoL Five-Dimension (Five-Level) questionnaire, QD: Quaque die, once daily
Source: [redacted] ([redacted])

EQ-VAS

EQ-VAS was summarised using continuous descriptive statistics for the May 31, 2019, data cut (Table 27). Due to the placement of PROs in the hierarchy of testing, all reported p-values are nominal (Schöffski et al. 2022).

Table 27 HRQoL EQ-VAS summary statistics [INVICTUS ITT population, May 31, 2019 data cut]

	Ripretinib 150 mg		Placebo		Ripretinib vs Placebo
	N	Mean (SD)	N	Mean (SD)	Effect size Hedges' g (95% CI)
Cycle 1, day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 1, day 15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 2, day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 6, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 7, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Ripretinib 150 mg		Placebo		Ripretinib vs Placebo
Cycle 8, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 9, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 10, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 11, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 12, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 13, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 14, day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 15, Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Notes: N= Number of patients with data at visit.
Abbreviations: CI: confidence interval, SD: standard deviation.
Source: [redacted] ([redacted]).

Change in EQ-VAS score at C2D1 from baseline between the treatment arms in INVICTUS was tested with a t-test (Table 28) (Schöffski et al. 2022). The ripretinib patients reported a higher EQ-VAS score on C2D1 than at baseline, with an increase of 3.7 (Schöffski et al. 2022). The score of placebo patients at that time point was lower than baseline with a decrease of 8.9 (nominal p value = 0.004).

Table 28 Mean change from baseline on C2D1 in EQ-VAS from INVICTUS [ITT population, May 31, 2019 data cut]

	Ripretinib (n=85) Mean (SD)	Placebo (n=43) Mean (SD)	Nominal p-value
Baseline	[redacted]	[redacted]	NR
C2D1	[redacted]	[redacted]	NR
Mean change from baseline to C2D1	3.7 (20.36)	-8.9 (19.31)	0.004

Numbers included for EQ-VAS analysis:
[redacted]
Abbreviations: C2D1: Day 1 of Cycle 2; SD: Standard deviation; NR: Not reported
Source: (Schöffski et al. 2022) [redacted]([redacted])

Further, the HRQoL scores (EQ-VAS as well as the disease-specific instrument) of patients treated with ripretinib remained stable as visualised in Figure 14 (Schöffski et al. 2022).

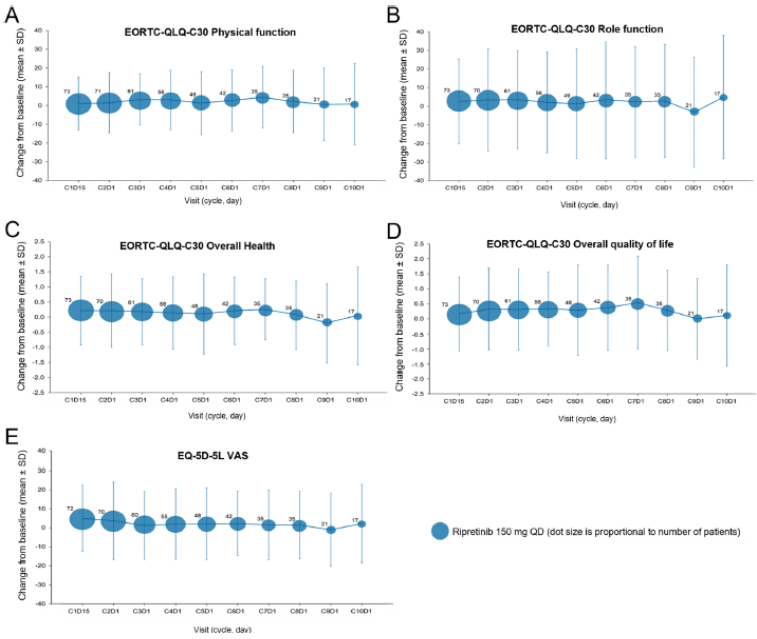


Figure 14 Change in quality-of-life scores (EQ-5D VAS and EOTRC-QLC-C30) relative to baseline in the ripretinib arm

Abbreviations: SD: standard deviation, QD: per day.
Source: (Schöffski et al. 2022)

In conclusion, the direct comparison of ripretinib versus placebo showed that ripretinib had a positive clinically significant effect on patients' quality of life compared to placebo. Consistent numeric differences in the INVICTUS study provided potential signals of HRQoL stabilisation or improvement in the ripretinib arm versus placebo arm across all HRQoL outcomes assessed. Whereby the effect of ripretinib also remained stable over time.

10.2 Health state utility values (HSUVs) used in the health economic model

Utility data used in the cost-effectiveness model include:

- Health state utility values
- AE disutilities
- Age-based utility multiplier

10.2.1 HSUV calculation

The utility values for health states PFS and PD on treatment in the model are based on EQ-5D-5L data, collected in the INVICTUS trial using the EQ-5D-5L instrument.

Health state utility values are assumed to apply at the start of the model; for every year subsequent to this, a multiplier is applied based on the ratio between the general

population utility values for the current age and the starting age. General population utility values for Denmark are sourced from the appendix to the Danish Medicines Council's methods guide (Danish Medicines Council 2021a).

To determine Danish utilities, only EQ-5D data from the uncensored ITT population was used. This includes the entire population for which progression was documented. In addition, only measures of visits were included in the analysis where patients had responded to all five dimensions of the EQ-5D-5L questionnaire. A Mixed Model for Repeated Measures (MMRM) analysis was then used to determine mean Danish utility by health condition and standard deviation. This analysis method was used to correct for correlation between measurements during visits per patient over time. To arrive at the Danish utilities, the Danish tariff described by Jensen et al. was applied (Jensen et al. 2021).

Three MMRM models were tested. Spatial power (Models 1 and 3) and compound symmetry (Model 2) covariance structures were investigated in order to account for any correlation across visits within each subjects-health state. The spatial power models incorporate the absolute distance (in continuous time) between visits within a subject as measured in units of 28 days (using the first observed PRO visit date within a health state for a given subject as the reference point).

Model 3 includes baseline utility and time (in months) since the subject's first PRO assessment as additional (continuous, linear) main effects in the model. Subjects with a missing baseline utility assessment were excluded from this analysis. A per-subject baseline utility measure was employed in this model, as opposed to a per-subject-health state baseline. The least squares means obtained from this model were jointly estimated at the overall baseline utility mean calculated across all subjects (i.e. not per health state) and at the mean time since their first PRO assessment (per health state).

Mathematically, the three MMRM models can be stated as follows:

Model 1: $Y_{ij} \sim Phase_{ij} + e_{ij}$, with $Cov(e_{ij}, e_{ik}) = \sigma_e^2 \rho^{d_{jk}}$

Model 2: $Y_{ij} \sim Phase_{ij} + e_{ij}$, with $Cov(e_{ij}, e_{ik}) = \sigma_e^2$

Model 3: $Y_{ij} \sim Phase_{ij} + Base_i + Time_{ij} + e_{ij}$, with $Cov(e_{ij}, e_{ik}) = \sigma_e^2 \rho^{d_{jk}}$

Where:

Y_{ij} = EQ-5D Danish utility value for the i^{th}subject at time *j*

$Phase_{ij}$ = Health state for the i^{th}subject at time *j* [PF or PD]

$Base_i$ = Baseline EQ-5D Danish utility value for the i^{th} subject [continuous]

$Time_{ij}$ = Time (months) since first EQ-5D utility assessment for the i^{th}subject at time *j* [continuous]

e_{ij} = error for the i^{th}subject at time *j*

σ_e^2 = Variance of the e_{ij}

ρ = Correlation

d_{ij} = Distance in time between month *j* and month *k*

The Kenward-Roger method of calculation of denominator degrees of freedom was used in all three models. Note that correlation between health states within subjects is not accounted for. It is assumed that this will have negligible impact in the estimation of the adjusted means and SDs.

Goodness of fit for all three models was assessed via the Akaike Information Criterion (AIC), Corrected AIC, and Bayesian Information Criterion (BIC). Model 2 resulted in the lowest statistic fit criteria and was hence chosen for deriving the health state utilities used in the model and displayed in Table 29.

10.2.1.1 Mapping

Not applicable.

10.2.2 Disutility calculation

See Section 10.3.4 and Appendix J.

10.2.3 HSUV results

An overview of the utility values used in the health economic analysis is presented in Table 29.

Table 29 Overview of health state utility values and disutilities

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
Progression free	[redacted]	EQ-5D-5L	DK	[redacted]
Progressed disease on treatment	[redacted]	EQ-5D-5L	DK	[redacted]
Disutilities	NA			

Notes: For Progression free health state: EQ-5D assessments prior to the date of progression (including Cycle 1 Day 1 visit) were included. For the Progressed disease health state: EQ-5D assessments on or after the date of BICR confirmed progression. A subject can contribute data to both PF and PD health states. Least squares mean and SD from MMRM adjusting for health state as a fixed effect and with a compound symmetry within-subject correlation structure per health state
Abbreviations: CI: Confidence interval, DK: Denmark, EQ-5D-5L: EuroQoL Five-Dimension (Five-Level), ITT: Intention to treat, MMRM: Mixed Model for Repeated Measures, NA: Not applicable, SD: Standard deviation.

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

In addition to the utilities derived from INVICTUS data, utilities were also sourced for the model from the GRID trial for the health state related to progressed off treatment.

10.3.1 Study design

GRID was a randomised, double-blind, placebo-controlled, crossover phase III trial designed to evaluate the efficacy and safety of regorafenib in patients with advanced GIST (Demetri et al. 2013, Poole et al. 2015). HRQoL was an exploratory endpoint.

Patients were randomised to receive either oral regorafenib 160 mg daily for 3 weeks of every 4-week cycle or a placebo in addition to BSC. Patients continued blinded treatment cycles until disease progression occurred, as confirmed by BICR, or withdrawal. Following unblinding, patients receiving placebo who experienced disease progression could be offered open-label regorafenib (crossover option). Whereas those randomised to regorafenib were able to continue open-label regorafenib upon local investigator discretion. Patients continued to receive regorafenib until further disease progression, upon which treatment with regorafenib was discontinued and treated with BSC alone.

In the publication by Poole and colleagues, HSUV for disease states for advanced GIST irrespective of treatment allocation in the GRID trial were estimated (Poole et al. 2015). The five clinical health states from this study were defined: Baseline, progression-free; On-treatment, progression-free; At first progression; Post-first progression; and Second progression. The EuroQol five-item questionnaire (EQ-5D-3L) was utilised. A single summary score was computed using the UK societal preference weighting algorithm.

10.3.2 Data collection

A total of 240 patients were enrolled; 41 patients (17.1 %) failed screening, and 199 (82.9 %) were randomized to double-blind treatment (n=123 to regorafenib + BSC and n=62 placebo +BSC) (Poole et al. 2015). The analysis set was considered to have baseline characteristics closely reflecting the ITT population.

The EQ-5D questionnaire was completed by patients at baseline (day 1 of cycle 1), at the first day of each cycle (every 4 weeks) during the first 3 months, at the first day of every other cycle (every 8 weeks) thereafter, and at the end of treatment visit. Questionnaires were completed at the start of a visit, before the patient saw their physician and before any study-related procedures, so that there was no influence on the responses.

In total, 185 patients had completed 803 EQ-5D questionnaires. There were no missing data from any of the questionnaires included in the analysis, and all observations were evaluable. 624 (77.7 %) observations were captured from patients in the health state "On-treatment, progression-free", 52 (6.5 %) were captured in state "At first progression", 112 (13.9 %) were captured in state "Post-first progression", and 15 (1.9 %) were captured in state "Second progression". There were 79 patients in total with baseline and observations in the two post-progression states.

10.3.3 HRQoL Results

The mean EQ-5D index score at baseline for all patients was 0.769 (SD 0.226) (Poole et al. 2015). There were no significant between-group differences at baseline (by treatment arm, line of therapy or disease progression).

A paired-sample comparison of the 77 patients that had observations at baseline and at a clinic visit following confirmed first disease progression found a statistically significant mean difference of -0.120 (p=0.001). The mean utility for subjects following second disease progression also was significantly lower than at baseline at -0.231 (p<0.001). The utility index scores for patients whose disease progressed is contained in Table 30.

Table 30: EQ-5D utility scores in first progression-free and post progression states for patients with advanced GIST whose disease progressed

Health state	N	Mean (SD)	Difference (95% CI) p-value
Baseline *	77	0.767 (0.221)	-0.120
First post-progression state	77	0.647 (0.343)	p= 0.001

*Baseline here refers to the first progression-free state

Abbreviations: CI: Confidence interval, SD: Standard deviation

Source: (Poole et al. 2015)

10.3.4 HSUV and disutility results

Table 31 presents utility values from other studies, than the study forming the basis for relative efficacy (INVICTUS) namely the GRID trial. External utility values for the progressed disease off treatment and progressed disease BSC were used. Because these are population-level point estimates, no mapping to Danish tariffs was performed, due to lack of credible methodology for carrying out the mapping exercise (population-level utility point estimates are non-linear transformations with respect to the tariff).

Table 31 Overview of health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
Progressed disease off treatment	0.647 [SD: 0.039]	EQ5D	UK	GRID trial (Poole et al. 2015)
Progressed disease BSC	0.647 [SD: 0.039]	EQ5D	UK	GRID trial (Poole et al. 2015)

Abbreviations: BSC: Best supportive care, CI: Confidence interval, HSUVs: Health state utility values, UK: United Kingdom.

The impact of AEs on HRQoL is captured as a one-off QALY loss applied in the first cycle of the model. Disutility of AEs is per event only and not related to duration of AE impact. The incidence of the AEs in each arm was multiplied by disutility values to obtain a total AE decrement for ripretinib and for BSC. Table 32 presents the values used in the health economics model originating from literature-based search; for an overview of literature-based health state utility values we refer to Appendix J.

Table 32 Overview of literature-based health state utility values [and disutilities]

Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs			
Study 1	NA		
Disutilities			
Anaemia	0.085	UK	The disutility for anaemia originated from Harrow et al. (2011), scaled to EQ-5D, as reported in Hoyle et al. (2013) (Hoyle et al. 2013, Harrow et al. 2011).
Abdominal pain	0.069	UK	(Doyle et al. 2008)
Hypertension	0.069	UK	(Doyle et al. 2008)

Abbreviations: EQ-5D: EuroQoL Five-Dimension, HSUVs: Health state utility values, NA: Not applicable, UK: United Kingdom.

11. Resource use and associated costs

Cost data used in the cost-effectiveness model include costs for drug acquisition, health care resource use, adverse events, transport costs and time spent by patients.

11.1 Medicine costs - intervention and comparator

Modelled acquisition costs are presented in Table 33. All costs were sourced from Medicinpriser.dk (Pharmaceutical purchasing prices) (Danish Medicines Agency 2024).

Ripretinib is available in 50 mg capsules and patients are assumed to receive 150 mg once daily. The list price per 30-day supply of ripretinib is 136,796.40 DKK. The ripretinib treatment duration is based on TTD data from the INVICTUS trial.

BSC costs were approximated from the concomitant medications taken in the BSC arm of the INVICTUS trial and used across both arms (Ripretinib and BSC). The BSC treatments are presented in Table 33 and were validated by a Danish clinician ([redacted]).

The RDI assumed for all treatments in the model is based on the INVICTUS trial. A scenario with 100% RDI was also explored in a scenario analysis.

Since all the pharmaceuticals included in the model are oral therapies except sodium chloride, no wastage was accounted for in the base case. A scenario was tested with a wastage of 25% for ripretinib over the entire time horizon.

Table 33 Medicine costs used in the model

Medicine	Strength	Relative dose intensity	Frequency	Vial sharing	Cost (DKK)
Ripretinib	50 mg	[redacted]	150 mg once daily		136 796.40
Paracetamol	500 mg	91.6%	500mg QDS		23.35
Oxycodone	80 mg	91.6%	100mg m/r BD		119.00
	20 mg				21.50
Fentanyl	50 mcg	91.6%	50mcg patch every 72 hours		198.50

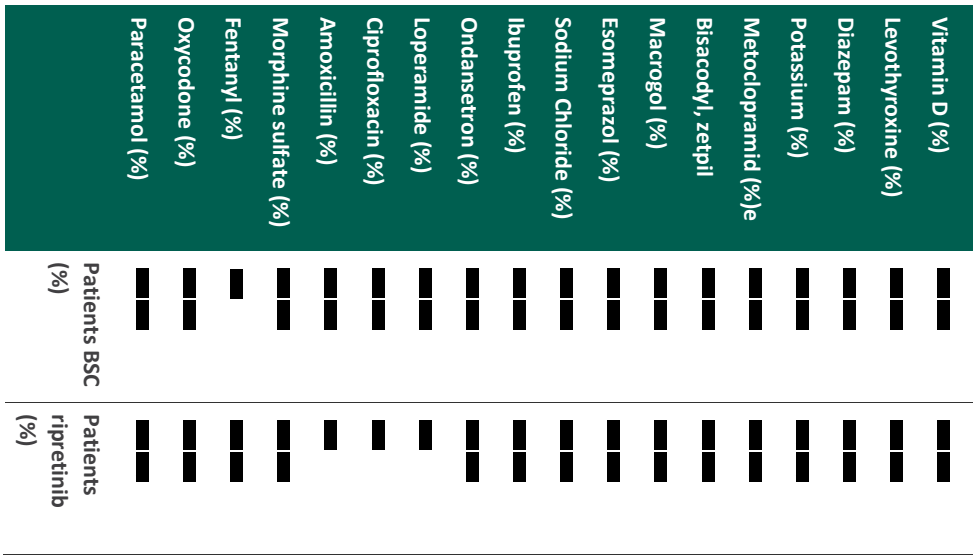
Medicine	Strength	Relative dose intensity	Frequency	Vial sharing	Cost (DKK)
Morphine sulfate	10 mg	91.6%	10mg every 4 hours		77.00
Amoxicillin	500 mg	91.6%	500mg TDS		524.76
Ciprofloxacin	500 mg	91.6%	500mg BD		15.00
Loperamide Hydrochloride	2mg	91.6%	6mg daily		110.09
Ondansetron	8 mg	91.6%	8mg every 12 hours		279.00
Ibuprofen	200 mg	91.6%	200mg TDS		12.87
Sodium Chloride	9mg/1ml, 1000 ml	91.6%	1500ml/24 hours once a month		159.53
Esomeprazol	40 mg	91.6%	40mg daily		47.05
Macrogol		91.6%	2 sachets daily		148.50
Bisacodyl, zetpil	10 mg	91.6%	zetpil 10 mg, BD		55.00
Metoclopramide	10 mg	91.6%	10mg TDS		76.58
Potassium Chloride tabs	750 mg	91.6%	750mg BD		84.00
Diazepam	2 mg	91.6%	2mg OD		87.85
Levothyroxine	50 mcg	91.6%	50mcg OD		26.49
Vitamin D	800 IU	91.6%	800IU OD		78.42

Abbreviations: BD: twice a day, IU: international units, m/r: modified release, OD: once a day, QDS: quater die sumendum, four times a day, TDS: three times a day, DKK: Danish Kronor.

11.2 Medicine costs – co-administration

Ripretinib is administrated as an add-on treatment to BSC. The proportion of patients receiving the treatments included in BSC are sourced from the INVICTUS trial and described in Table 34 for both arms. The costs of BSC treatments are included in Table 33.

Table 34 Proportion of patients receiving BSC treatments



Abbreviations: BSC: Best supportive care.

Source: [redacted] ([redacted])

11.3 Administration costs

The analysis assumes there are no administration costs for ripretinib (oral drug) or BSC (Table 35). The only BSC medication that requires intravenous infusion is sodium chloride, for which a single dose is assumed per cycle, received by 11.6% and 16.5% of patients in the BSC only arm and ripretinib + BSC arm, respectively. The impact of including the costs for intravenous infusion would be negligible and has therefore been assumed to be zero.

Table 35 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
Oral	NA	NA	NA	NA

Abbreviations: DKK: Danish Kronor, NA: Not applicable.

11.4 Disease management costs

Disease management costs included in the model were based on the most recent NICE GIST technology appraisal, TA488 (NICE 2017b), since no other information is available. These resources and frequencies were then validated by a Danish clinician and adjusted to align with clinical practice in Denmark ([redacted]). The resulting resource use and unit costs used in the model are described in Table 36.

Table 36 Disease management costs for regular tests/resources for ripretinib used in the model

Activity	Frequency ripretinib	Frequency BSC	Unit cost [DKK]	DRG code / type of test/visit	Reference
CT scan	PFS: 4.3/year PD(t): 4.3/year PD: 0	PFS: 0 PD: 0	2585,00 DKK	30PR06 - CT-scanning, kompliceret	DRG 2024 (Sundhedsdatastyrelsen 2024)
MRI scan	PFS: 2.6/year PD(t): 2.6/year PD: 0	PFS: 0 PD: 0	2511,00 DKK	30PR02 - MR-scanning, kompliceret	DRG 2024 (Sundhedsdatastyrelsen 2024)
Full blood count	PFS: 8.2/year PD(t): 8.2/year PD: 0	PFS: 0 PD: 0	22,64 DKK	Blod	Taktskort 2024 (Laeger.dk 2024b)
Liver function test	PFS: 8.2/year PD(t): 8.2/year PD: 0	PFS: 0 PD: 0	22,64 DKK	Blod	Taktskort 2024 (Laeger.dk 2024b)
Outpatient vists	PFS: 8.5/year PD(t): 8.5/year PD: 0	PFS: 6.6/year PD: 0	156,39 DKK	0101 Konsultation	Honorartabel (Laeger.dk 2024a)
Palliative resection	Once, in PF and PD state	Once, in PF and PD state	89 006,00 DKK	26MP47 - Specialiseret Palliativ indsats, Øvrig	DRG 2024 (Sundhedsdatastyrelsen 2024)
Palliative radiotherapy	Once, in PF and PD state	Once, in PF and PD state	2709,00 DKK	27MP04 - Strålebehandling, kompleks, 1 fraktion	DRG 2024 (Sundhedsdatastyrelsen 2024)

Abbreviations: CT: Computed tomography, DKK: Danish Kronor, DRG: Diagnosis Related Group, MRI: Magnetic Resonance Imaging, PD: Progressive disease, PFS: Progression free survival.

11.4.1 One-off health state resource use

One-off costs are included in the first cycle in both arms of the model for tests taken by a proportion of patients before treatment, in addition to palliative surgical resection and palliative radiotherapy given to relieve or prevent symptoms (Table 37). [redacted] most patients that are treated with ripretinib will not have additional tests performed prior to the start of treatment since these tests have already been received at progression in earlier lines. Hence, the assumption that [redacted] of the patients receive tests prior to treatment with ripretinib is a conservative assumption. A scenario analysis was performed, assuming that [redacted] of the patients receive tests prior to treatment with ripretinib.

Table 37 Proportion of patients receiving resource use prior to treatment and palliative care interventions

Activity	Proportion of patients ripretinib	Proportion of patients BSC
CT scan	90%	0%
MRI scan	0%	0%
Full blood count	90%	0%
Liver function test	90%	0%
Palliative resection	PF: 10%, PD: 10%	PF: 10%, PD: 10%
Palliative radiotherapy	PF: 20%, PD: 20%	PF: 20%, PD: 20%

Abbreviations: BSC: Best supportive care, CT: Computed tomography, MRI: Magnetic resonance imaging, PD: Progressive disease, PF: Progression-free.

11.5 Costs associated with management of adverse events

Costs of treatment-related AEs were included in the evaluation and modelled via the incidence of grade 3-4 AEs. Grade 3-4 TEAEs occurring ≥5% in either treatment arm of INVICTUS were included in the evaluation as they are likely to be associated with costs that will affect decision making. Unit costs for AEs included in the model were sourced from Danish DRG tariffs (Sundhedsdatastyrelsen 2024) and are presented in Table 38. The cost of AEs were included in the model as one-time cost in the first cycle. The proportion of patients experiencing each AE and incurring said costs are presented above in Table 22.

Table 38 Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff
Anaemia	16MA10	27 121
Abdominal pain	06MA11	7 818

	DRG code	Unit cost/DRG tariff
Hypertension	DRG 05MA11	18 261

Abbreviations: DRG: Diagnosis-related group.

11.6 Subsequent treatment costs

No subsequent treatments are included. Table 39 is therefore blank.

Table 39 Medicine costs of subsequent treatments

Medicine	Strength	Package size	Pharmacy purchase price [DKK]	Relative dose intensity	Average duration of treatment
NA					

Abbreviations: NA: Not applicable..

11.7 Patient costs

The model accounts for the cost of transportation and the time patients spend on visits to the hospital in relation to CT-scans, MRI and outpatient visits. It was assumed that a full blood count and a liver test can be performed at the same time as an outpatient visit. Hence, there is no additional transportation and patient time cost for full blood counts and liver tests. For transportation cost, an average cost of 140 DKK was assumed per hospital visit in accordance with the DMC's catalogue of unit costs (Danish Medicines Agency 2023). The time spent on a hospital visit is assumed to be 1 hour on average with a cost of 203 DKK per hour in line with the DMC's catalogue of unit costs (Danish Medicines Agency 2023). The detailed time and costs are presented in Table 40.

Table 40 Patient costs used in the model

Activity	Time spent [minutes, hours, days]
CT-scan	1 hour
MRI	1 hour
Outpatient visit (including full blood count and liver test)	1 hour

Abbreviations: CT: Computed tomography, MRI: Magnetic resonance imaging.

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

End-of-life costs are included in the base case analysis amounting to 91 620 DKK per event. This cost is based on an event duration of 30 days using unit cost “Død eller overflyttet inden for 1 dag” (DRG-takser 2024 (DRG 15MP01")).

12. Results

12.1 Base case overview

An overview of the base case where ripretinib is compared against BSC is in Table 41.

Table 41 Base case overview

Feature	Description
Comparator	BSC
Type of model	Partitioned survival model
Time horizon	40 years (lifetime)
Treatment line	4L. Subsequent treatment lines not included.
Measurement and valuation of health effects	HRQoL measured with EQ-5D-5L in study the INVICTUS study. Danish population weights were used to estimate health-state utility values. Utility values for the progressed disease off treatment and progressed disease BSC health states were sourced from GRID trial (Poole et al. 2015).
Costs included	Drug acquisition costs Disease management costs Costs of adverse events Patient costs
Dosage of medicine (ripretinib)	150 mg ripretinib orally, once daily.
Average time on treatment	[redacted]
Parametric function for PFS	Ripretinib: log-normal BSC: log-normal
Parametric function for OS	Ripretinib: log-normal BSC: log-normal
Inclusion of waste	No

Feature	Description
Average time in model health state	
PF	[redacted]
PD on treatment	[redacted]
PD off treatment	[redacted]
PD BSC	[redacted]

Abbreviations: BSC: Best supportive care, OS: Overall survival, PFS: progression-free survival.

12.1.1 Base case results

The base case results are presented in Table 42.

Table 42 Base case results, discounted estimates

	Ripretinib (DKK)	BSC (DKK)	Difference (DKK)
Medicine costs	[redacted]	8 578	[redacted]
Medicine costs – co-administration	NA (included in medicine costs)	NA	NA
Administration	0	0	0
Disease management costs	[redacted]	[redacted]	[redacted]
Costs associated with management of adverse events	[redacted]	[redacted]	[redacted]
Subsequent treatment costs	NA	NA	NA
Patient costs	[redacted]	[redacted]	[redacted]
Palliative care costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
Life years gained (health state PF)	[redacted]	[redacted]	[redacted]
Life years gained (health state PD)	On treatment: [redacted] Off treatment: [redacted]	[redacted] [redacted]	[redacted] [redacted]
Total life years	[redacted]	[redacted]	[redacted]

	Ripretinib (DKK)	BSC (DKK)	Difference (DKK)
QALYs (PF)	[redacted]	[redacted]	[redacted]
QALYs (PD)	On treatment: [redacted] Off treatment: [redacted]	[redacted] [redacted]	[redacted]
QALYs (adverse reactions)	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental costs per life year gained		[redacted]	
Incremental cost per QALY gained (ICER)		[redacted]	

Abbreviations: BSC: Best supportive care, ICER: Incremental cost-effectiveness ratio, QALY: Quality-adjusted life-years.

12.2 Sensitivity analyses

Both deterministic sensitivity analyses (DSA) and probabilistic sensitivity analyses (PSA) were performed. More details regarding the PSA can be found in Appendix G.

Deterministic sensitivity analyses

Table 43 and Figure 15 show the results of the performed one-way sensitivity analyses where the inputs were varied according to 95% confidence interval or, if confidence interval was not available, with an arbitrary range of +/- 20%. The ten most influential parameters are presented in Table 43. Table 44 presents scenario analyses where the impact of alternative values on a set of selected parameters were analysed.

Table 43 One-way sensitivity analyses results

Parameter	ICER at lower value of parameter (DKK/QALY)	ICER at higher value of parameter (DKK/QALY)	Difference in ICER at lower and higher value os parameter (DKK/QALY)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Parameter	ICER at lower value of parameter (DKK/QALY)	ICER at higher value of parameter (DKK/QALY)	Difference in ICER at lower and higher value os parameter (DKK/QALY)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DKK: Danish Crowns, ICER: Incremental cost-effectiveness ratio, QALY: Quality-adjusted life-years; PFS, progression-free survival; OS, overall survival, TTD, time to discontinuation.

Figure 15 [redacted]

Table 44 Scenario analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case			[redacted]	[redacted]	[redacted]
40-year time horizon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient mean age: 60.1 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
	[redacted]	[redacted]			
Mean percentage males: 57%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Extrapolation functions: Lognormal: Ripretinib PFS, OS & BSC PFS, OS Log-logistic: Ripretinib TTD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cross-over adjustment for open-label period with “two-stage adjusted simple with recensoring”	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RDI based on INVICTUS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No wastage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Health state utility PDOn based on INVICTUS ( )					
Health state utility PDOff & PD BSC based on GRID (0.647)					
No CT-scans regularly in health states PD with no treatment					
% of patients receive palliative radiotherapy in PF and PD					
AE disutilities included					
End of life cost included					

Abbreviations: AE: Adverse event, BSC: Best-supportive care, CT: Computed tomography, DKK: Danish Crowns, ICER: Incremental cost-effectiveness ratio, OS,: Overall survival, PF: Progression free, PD: Progressed disease, PFS: Progression-free survival; QALY: Quality adjusted life years, RDI: Relative dose intensity, TTD: Time to discontinuation

Probabilistic sensitivity analyses

The PSA was conducted using 1 000 Monte Carlo simulations to account for parameter uncertainty. To account for correlated parameters, a Cholesky decomposition was used to simulate correlated parameters within distributions. The results are tabulated in Table 45. The scatter plot (Figure 16) of incremental costs vs. QALYs gained shows a cloud of points centred around the mean ICER. The points are more widely spread around QALYs gained than around incremental costs, indicating that the cost-effectiveness is more sensitive to parameter uncertainty relating to QALYs.

Table 45 Probabilistic results

	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	[redacted]	[redacted]	[redacted]
Probabilistic results	[redacted]	[redacted]	[redacted]

Abbreviations: DKK: Danish Crowns, ICER: Incremental cost-effectiveness ratio, QALY: Quality-adjusted life-years.

Figure 16: Incremental cost-effectiveness plane

Abbreviations: BSC: Best supportive care, DKK: Danish Kronor, PSA: Probablistic sensitivity analysis, QALY: Quality adjusted life year.

13. Budget impact analysis

Table 46 presents the number of new patients that are expected to be treated over a 5-year period. The expected budget impact is presented in Table 47.

Number of patients (including assumptions of market share)

Table 46 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
	Recommendation				
Ripretinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Non-recommendation				
Ripretinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC: best supportive care.

Budget impact

Table 47 Expected budget impact of recommending the medicine for the indication

	Year 1 (DKK)	Year 2 (DKK)	Year 3 (DKK)	Year 4 (DKK)	Year 5 (DKK)
Ripretinib is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ripretinib is NOT recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DKK: Danish Crowns.

14. List of experts

[redacted]

15. Reference list

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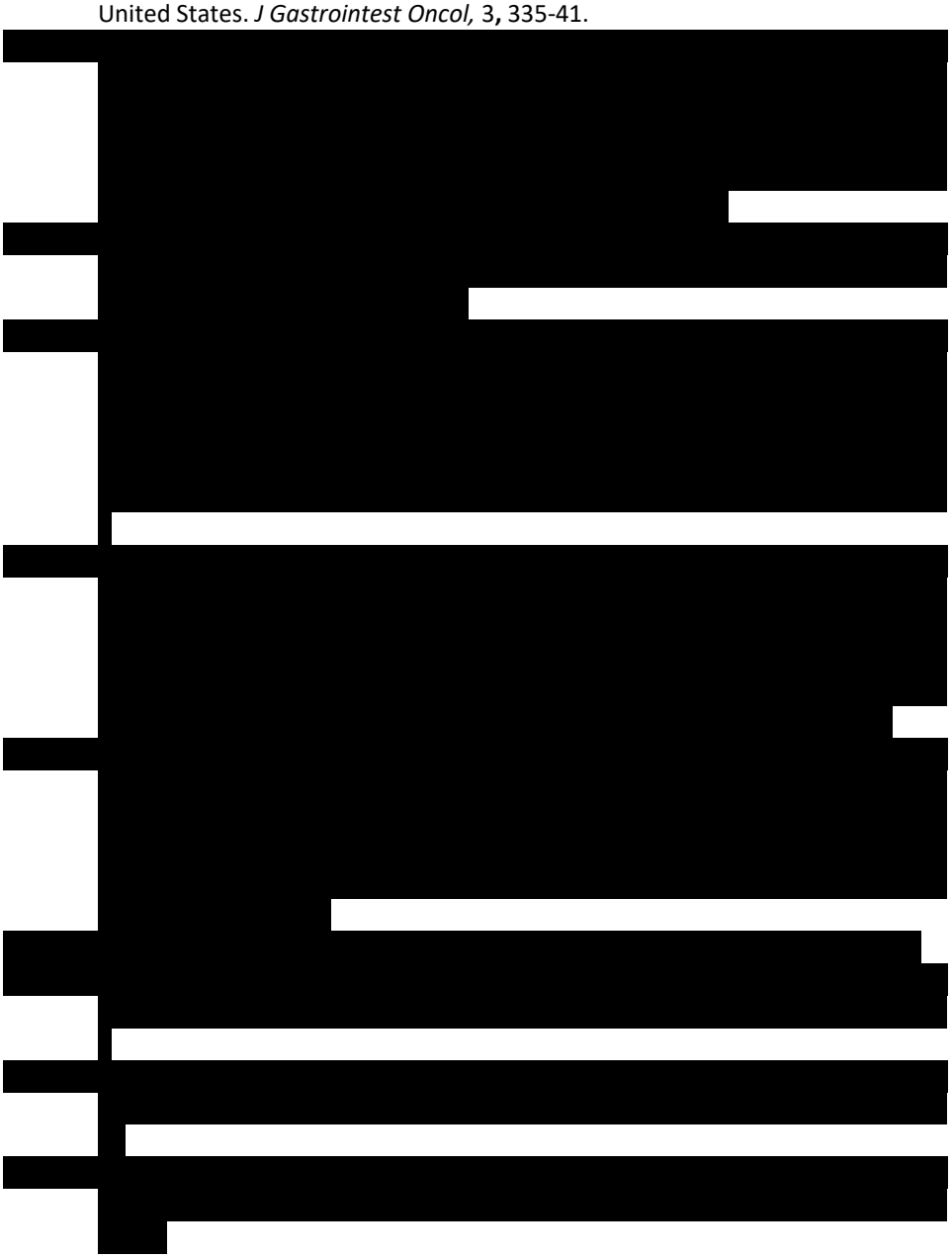

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Appendix A. Main characteristics of studies included

Table 48 Main characteristic of studies included

Trial name: Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial	**NCT number: NCT03353753**
Objective	The objective of the study was to compare the efficacy and safety of ripretinib with placebo in patients with previously treated, advanced gastrointestinal stromal tumours.
Publications – title, author, journal, year	Bauer, S., Heinrich, M. C., George, S., Zalcberg, J. R., Serrano, C., Gelderblom, H., Jones, R. L., Attia, S., D'amato, G., Chi, P., Reichardt, P., Meade, J., Su, Y., Ruiz-Soto, R., Blay, J. Y., Von Mehren, M. & Schöffski, P. 2021. Clinical Activity of Ripretinib in Patients with Advanced Gastrointestinal Stromal Tumor Harboring Heterogeneous KIT/PDGFRA Mutations in the Phase III INVICTUS Study. Clin Cancer Res, 27, 6333-6342. Blay, J. Y., Serrano, C., Heinrich, M. C., Zalcberg, J., Bauer, S., Gelderblom, H., Schöffski, P., Jones, R. L., Attia, S., D'amato, G., Chi, P., Reichardt, P., Meade, J., Shi, K., Ruiz-Soto, R., George, S. & Von Mehren, M. 2020. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol, 21, 923-934. Schöffski, P., George, S., Heinrich, M. C., Zalcberg, J. R., Bauer, S., Gelderblom, H., Serrano, C., Jones, R. L., Attia, S., D'amato, G., Chi, P., Reichardt, P., Becker, C., Shi, K., Meade, J., Ruiz-Soto, R., Blay, J. Y. & Von Mehren, M. 2022. Patient-reported outcomes in individuals with advanced gastrointestinal stromal tumor treated with ripretinib in the fourth-line setting: analysis from the phase 3 INVICTUS trial. BMC Cancer, 22, 1302. Von Mehren, M., Heinrich, M., George, S., Zalcberg, J. R., Bauer, S., Gelderblom, H., Schöffski, P., Serrano, C., Jones, R., Attia, S., D'amato, G., Chi, P., Reichardt, P., Meade, J. N., Reichert, V. L., Shi, K., Ruiz-Soto, R. & Blay, J.-Y. 2021. Ripretinib as ≥4th-line treatment in patients with advanced gastrointestinal stromal tumor: Long-term update from the phase III INVICTUS study. Annals of Oncology, 32, S1120-S1121. Zalcberg, J. R., Heinrich, M. C., George, S., Bauer, S., Schöffski, P., Serrano, C., Gelderblom, H., Jones, R. L., Attia, S., D'amato, G., Chi, P., Reichardt, P., Somaiah, N., Meade, J., Reichert, V., Shi, K., Sherman, M. L., Ruiz-Soto, R., Von Mehren, M. & Blay, J. Y. 2021. Clinical Benefit of Ripretinib Dose Escalation After Disease Progression in Advanced Gastrointestinal Stromal Tumor: An Analysis of the INVICTUS Study. Oncologist, 26, e2053-e2060.

Trial name: Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial	NCT number: NCT03353753
Study type and design	The trial was phase 3 with double-blinding. Patients were randomly assigned 2:1 through interactive stratified permuted randomisation (daily oral ripretinib 150mg or placebo). Patients, investigators, research staff, and the sponsor study team were masked to a patient's treatment allocation until the BICR showed progressive disease for the patient. Crossover was allowed in case of disease progression. The study was completed on 11/05/2024.
Sample size (n)	129 patients
Main inclusion criteria	Key inclusion criteria were patients aged 18 years or older with a diagnosis of gastrointestinal stromal tumour with at least one measurable lesion according to modified Response Evaluation Criteria in Solid Tumours version 1.1 (mRECIST 1.1).
Main exclusion criteria	Key exclusion criteria included anticancer therapy received within 14 days or five times the half-life (whichever was longer) before the first dose of study drug.
Intervention	85 patients received oral ripretinib 150 mg once a day plus best supportive for 28-day cycles until they developed progressive disease, experienced unacceptable toxic effects, or withdrew consent.
Comparator(s)	44 patients received a placebo once a day plus best supportive for 28-day cycles until they developed progressive disease, experienced unacceptable toxic effects, or withdrew consent.
Follow-up time	At the primary data cut-off 31 May 2019 the median follow-up time in the double-blind period was 6.3 months (IQR 3.2-8.2) for the ripretinib group or 1.6 months for the placebo group.
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** The primary efficacy endpoint was progression-free survival (the interval between the date of randomisation to the date of documented progressive disease or death due to any cause) according to mRECIST 1.1, as assessed by BICR. Other secondary endpoints included in the application were overall survival (the interval between the date of randomisation and the date of death from any cause), time to treatment discontinuation, QoL, and safety. QoL scores were based on EQ-5D-5L. This is a validated, standardised, patient-completed questionnaire used extensively in clinical cancer

	studies, for which validated translations were provided for sites in non-English-speaking countries. **Other endpoints:** Other secondary endpoints not included in this application include objective response rate (confirmed complete response and partial response assessed by BICR, time to progression (the interval between the date of randomisation and the earliest documented evidence of progressive disease based on independent radiological review), time to best response, progression-free survival by investigator assessment (the interval between the date of randomisation and the earliest documented evidence of progressive disease based on investigator evaluation or death from any cause). QoL was also assessed against four sections of the EORTC QLQ-C30 scale: physical function, role function, overall health, & overall quality of life. This cancer-specific tool is a validated, standardised, patient-completed questionnaire. Validated translations were provided in non—English-speaking countries.
Method of analysis	The primary analysis was done in the intention-to-treat population and safety was assessed in patients who received at least one dose of study drug. Time-to-event data (progression-free survival, overall survival, time to progression, and time to best response) were summarised using the Kaplan-Meier method. A two-sided stratified log-rank test (0·05 significance level) was used to evaluate treatment difference. Hazard ratios (HRs) were obtained from a Cox regression model, and the 95% CIs were obtained using the Wald method. Hierarchical testing was conducted for secondary endpoints. The EORTC QLQ-C30 was summarized by scale, with scoring done in two steps with initial calculation of the average of the items that contribute to the scale. This was used as the raw score for the scale, to which a linear transformation was applied to standardize it, so that scores ranged from 0 to 100. The EQ-5D-5L VAS was summarized using continuous descriptive statistics. Statistical comparisons between treatment arms were carried out on cycle 2, day 1 (C2D1, prespecified endpoint) for two functioning scales and the EQ-5D-5L VAS. For selected domains from the EORTC QLQ-C30 (physical function, role function, overall health, overall QoL), analysis of covariance (ANCOVA) models were built for change from baseline to C2D1, with the stratification factors as factors. For the EQ-5D-5L VAS, a t-test was performed between the ripretinib and placebo group for their change from baseline to C2D1 scores. In exploratory analyses, generalised estimating equation models were created to compare patients with and without alopecia. Models were built for each of the five PROs for ripretinib patients using repeated measures models across visits. For patients with alopecia, cycles 1 and 2 were excluded to account for the median time of alopecia onset.

Trial name: Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial	NCT number: NCT03353753
	Covariates were sex, alopecia (yes/no), and ECOG score at baseline. When there was no end date available for the TEAE, the event was coded conservatively as having extended to the last visit of the double-blind period. Due to the placement of PROs in the hierarchy of testing, all p-values reported in the study were nominal. Time to discontinuation analyses were conducted on the safety population among patients treated with ripretinib and summarised with the Kaplan Meier method.
Subgroup analyses	Pre-specified subgroup analyses were performed for the primary and key secondary efficacy endpoints for the following: • Age (18 – 64 vs 65 – 74 vs 75 years or older) • Gender (Male vs female) • Race (White vs non-White vs not reported) • Region (US vs non-US) • Screening ECOG (0 vs 1/2) • Number of prior therapies (3 vs ≥4)
Other relevant information	None

Abbreviations: BICR: Blinded independent central review, CI: Confidence interval, C2D1: Cycle 2 Day 1, ECOG: Eastern Cooperative Oncology Group, EORTC-QLQ-C30: European Organization for Research and Treatment of Cancer Questionnaire, EQ-5D-5L: EuroQoL Five-Dimension Five-Level questionnaire, IQR: Interquartile range, N: Number, PRO: Patient-reported outcome, QoL: Quality of life, TEAE: Treatment-emergent adverse event, US: United States, VAS: Visual analogue scale

Appendix B. Efficacy results per study

Results per study

Key efficacy results from INVICTUS from the primary data-cut (31 May 2019) and the later data-cut (15 January 2021) underlying the health economic model are contained in Table 49. In addition to the table, figures from the primary data analysis of INVICTUS follow with Figure 17 presenting the KM curve of PFS as confirmed by BICR for the primary analysis and Figure 18 displaying the KM curve of OS (Blay et al. 2020). More detailed findings from INVICTUS regarding ORR follow.

Table 49 Results per study - INVICTUS

Results of Phase 3 Study of Ripretinib vs Placebo in Advanced GIST Patients Who Have Been Treated With Prior Anticancer Therapies (INVICTUS) (NCT03353753)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Progression-free survival											
Progression-free survival [DCO 31 May 2019]	Ripretinib	85	6.3 months (95% CI 4.6 to 6.9)	5.3	4.2 to 6.5	<0.0001	HR: 0.15	0.9 to 0.25	p<0.0001	ITT population. PFS with progression confirmed by BICR. Summarised using the Kaplan-Meier method and associated two-sided 95% CI. HRs were obtained from a Cox regression model, and the 95% CIs were obtained using the Wald method. The proportional hazards assumption was examined by visual inspection of the log (-log) plot	(Blay et al. 2020)
	Placebo	44	1.0 months (95% CI 0.09 to 0.25)								

Progression-free survival [DCO 09 March 2020]	Ripretinib	85	6.3 months (95% CI 1.6 to 8.1)	NR	NR	NR	HR 0.16	NR	NR	ITT population. PFS with progression confirmed by BICR. Same methods as above but updated with data as of March 2020.	(Zalcberg et al. 2020)
	Placebo	44	1.0 months (95% CI 0.9 to 1.7)								
Progression-free survival [DCO 15 January 2021]	Ripretinib	85	6.3 months (95% CI 4.6 to 8.1)	NR	NR	NR	HR 0.16	0.10 to 0.27	<0.0001	ITT population. PFS with progression confirmed by BICR. Summarised using the Kaplan-Meier method and associated two-sided 95% CI. HRs were obtained from a Cox regression model, and the 95% CIs were obtained using the Wald method. Number of patients with event: Ripretinib n= 71 (84%) Placebo n=37 (84%) PFS rate at 18 months: Ripretinib: 11.8 (95%CI 5.6 to 20.6) Placebo: NE	(von Mehren et al. 2021)
	Placebo	44	1.0 months (95% CI 0.9 to 1.7)								
Objective response rate											
Objective response rate	Ripretinib	85	9.4% (95% CI 4.2 to 17.7)	9.4%	2.7 to 16.1	0.0504	NR	NR	NR	ITT population. Objective response rate (confirmed complete response and partial response assessed by BICR) was analysed by an unstratified two-sided	(Blay et al. 2020)
	Placebo	44	0%								

[DCO 31 May 2019]										Fisher's exact test (using a 0.05 significance level) to evaluate treatment difference, and the 95% CI of the treatment difference was calculated with the Newcombe method. Changes in tumour measurements were confirmed by repeat assessments that were performed at least four weeks (allowing a minus three days window). After the criteria for response are first met. This analysis included assessments prior to an event or censoring under the primary PFS analysis. Patients with unknown or missing response were categorised as non-responders and were included in the denominator when calculating the proportion.	
Objective response rate **[DCO 15 January 2021]**	Ripretinib	85	10 (11.8%) (95% CI: 5.8 to 20.6)	NR	NR	NR	NR	NR	NR	ITT population. Objective Response Rate is defined as the proportion of patients with a confirmed complete response or partial response based on BICR and during the initial assigned study treatment. 95% CI is exact binomial CI. 95% CI is Newcombe Score CI of the difference in objective response rate between the treatment	(von Mehren et al 2021)
	Placebo	44	0 (95% CI 0.0 to 8.0)								

										arms. P-value is based on Fisher's exact test.	
Overall survival											
Overall survival [DCO 31 May 2019]	Ripretinib	85	15.1 months (95% CI 12.3 to 15.1)	8.5	4.5 to 12.5	<0.0001	HR: 0.36	0.21 to 0.62	NR	ITT population. Summarised using the Kaplan-Meier method and associated two-sided 95% CI. HRs were obtained from a Cox regression model, and the 95% CIs were obtained using the Wald method. The proportional hazards assumption was examined by visual inspection of the log (-log) plot. Owing to hierarchical testing procedure the OS could not be formally tested for statistical significance as the ORR was not significant.	(Blay et al. 2020)
	Placebo	44	6.6 months (4.1 to 11.6)								
Overall survival [DCO 09 March 2020]	Ripretinib	85	Not reached (95% CI 13. 1 to NE)	NR	NR	NR	HR: 0.43	NR	NR	ITT population. Median OS. Upon disease progression determined by BICR, patients on placebo could cross over to ripretinib 150 mg QD. Same methods as above but updated with data as of March 2020.	(Zalcberg et al. 2020)
	Placebo	44	6.3 months (95% CI: 4.1 to 10.0)								
Overall survival	Ripretinib	85	18.2 months (95% CI 13.1 to 30.7)	NR			HR: 0.41	0.26 to 0.65	0.0002	Patient groups are based on the treatment initially assigned (ITT).	(von Mehren et al. 2021)

[DCO 15 January 2021]	Placebo	44	6.3 months (95% CI 4.1 to 10.1)	Number of Patients with Event Placebo: 36 (82%) Ripretinib: 46 (54%) Number of Patients Censored Placebo: 8 (18%); Ripretinib: 39 (46%) Kaplan-Meier Estimate of Overall Survival. P-value is based on 2-sided stratified Log Rank test. Cox regression model includes treatment and randomisation stratification factors as fixed factors. 95% CI based on Wald Method. Overall survival rate at 24 Months Placebo: 19.8% (95% CI: 9.4 to 33.0) Ripretinib: 42.8% (31.5 to 53.7)

Abbreviations: BICR: Blinded independent central review, CI: Confidence interval, DCO: data-cut off, questionnaire, HR: Hazard ratio, ITT: Intention to treat, NE: Not evaluable; NR: Not reported, OS: Overall survival, PFS: Progression-free survival, QD: Quaque die, once daily, VAS: Visual analogue scale.

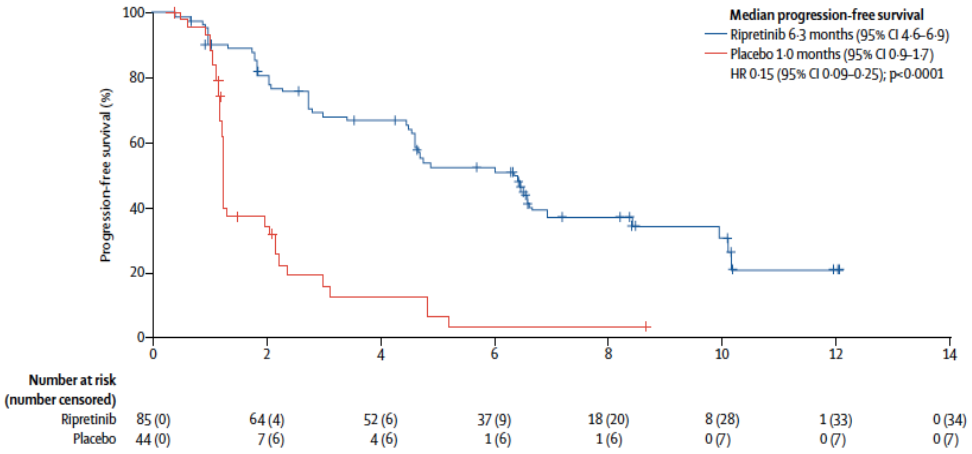


Figure 17 Kaplan-Meier PFS curve, primary analysis (ITT population, data cut 31 May 2019)

Abbreviations: CI: Confidence interval, HR: Hazard ratio, ITT: Intention to treat.
Source: (Blay et al. 2020).

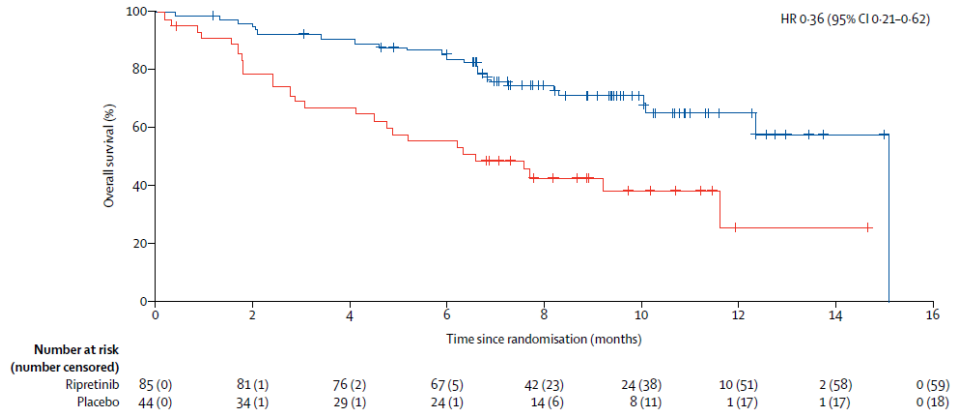


Figure 18 Kaplan-Meier OS curve, primary analysis (ITT population, data cut 31 May 2019)

Abbreviations: CI: Confidence interval, HR: Hazard ratio, ITT: Intention to treat.
Source: (Blay et al. 2020).

ORR was a key endpoint in INVICTUS given that it reflects disease stability. Six weeks after randomisation, 66% of ripretinib and 20% of placebo patients had stable disease. After 12 weeks, these proportions were 47% and 5%, respectively (Table 50) (Blay et al. 2020). After 12 weeks, nearly half of ripretinib patients still had stable disease. Yet, in the placebo group, only a few individuals had stable disease after twelve weeks.

Table 50 Objective response rate and duration of response per BICR in the primary and follow-up analysis

	Ripretinib (n=85)	Placebo (n=44)	P-value

	n (%)	95% CI	n (%)	95% CI	
Primary analysis (Data cut 31/05/2019)					
Confirmed ORR	8 (9%)	4%-18%	0 (0%)	0%-8%	0.0504
Complete response	0 (0%)	0%-4%	0 (0%)	0%-8%	-
Partial response	8 (9%)	4%-18%	0 (0%)	0%-8%	-
Stable disease (6 weeks)	56 (66%)	55%-76%	9 (20%)	10%-35%	-
Stable disease (12 weeks)	40 (47%)	36%-58%	2 (5%)	1%-6%	-
Progressive disease	16 (19%)	11%-29%	28 (64%)	48%-78%	-
Not evaluable	4 (5%)	-	3 (7%)	-	-
No evaluation	1 (1%)	-	4 (9%)	-	-
Follow-up analysis (Data cut 15/01/2021)					
Confirmed ORR	10 (11.8%)	5.8%-20.6%	0 (0%)	0%-8.0%	[redacted]

Abbreviations: BICR: Blinded independent central review, CI: Confidence interval, n: number, NE: Not estimable, OR: Objective response, ORR: Objective response rate.
Source: Primary analysis (Blay et al. 2020) and follow up analysis ([redacted], von Mehren et al. 2021).

Appendix C. Comparative analysis of efficacy

Not applicable owing to the randomized clinical trial of ripretinib vs the relevant comparator.

Table 51 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		

Appendix D. Extrapolation

D.1 Extrapolation of overall survival

D.1.1 Data input

Data informing overall survival is collected in the INVICTUS trial (see Section 6.1.1.).

D.1.2 Model

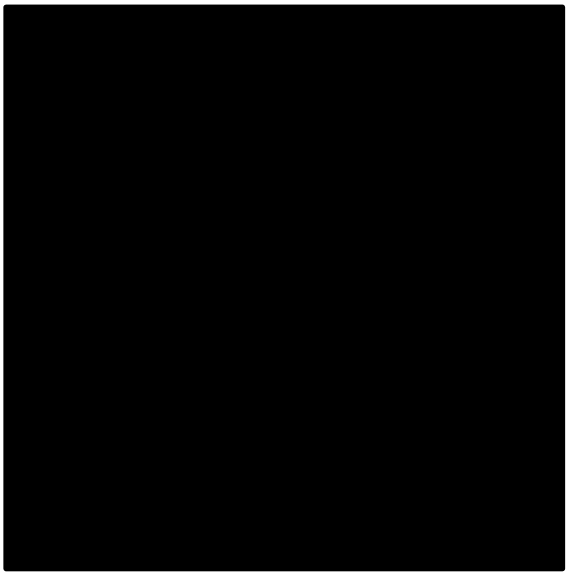
As per the study design for INVICTUS, study drug treatment was unblinded upon disease progression and patients randomly assigned to placebo were given the option to crossover to receive open-label ripretinib. As the true survival associated with placebo will be confounded by the benefits of crossover onto open-label ripretinib, conventional survival analysis will underestimate the survival benefit associated with ripretinib. The model used to adjust for cross-over was the standard two-stage cross-over adjustment model (see section D.1.9).

D.1.3 Proportional hazards

Following completion of the cross over adjustment, statistical tests were conducted to test if the PH assumption holds between the two treatment arms of INVICTUS within the observed trial follow-up period. Two statistical tests were conducted: the complementary log-log plot, and the Schoenfeld residuals test. The outcomes of these statistical tests were used to determine whether the null hypothesis, that is, that PH between treatment arms holds, could be rejected.

Inspection of the log-cumulative hazards ([redacted]) and Schoenfeld residual plot ([redacted]) suggests that it would be reasonable to accept the PH assumption. [redacted].

Figure 19 [redacted]



Abbreviations: BSC: Best supportive care, OS: Overall survival.

Figure 20 [redacted]

Abbreviations: BSC: Best supportive care, KM: Kaplan-Meier.

D.1.4 Evaluation of statistical fit (AIC and BIC)

A summary of the goodness-of-fit statistics for the PFS extrapolations is presented in Table 52.

Table 52 [redacted]

Distribution	Ripretinib		BSC (Simple 2SRC)		Combined	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 2SRC: Two-stage adjustment with recensoring, AIC: Akaike information criterion, BIC: Bayesian information criterion, BSC: Best supportive care.

The combined AICs were calculated but were too close to be used to make a judgement for the best statistical fit alone. As such, the [redacted] distribution was selected as the base-case curve used for OS extrapolation, as having one of the lowest combined AICs and best visual fit (see section D.1.5.).

D.1.5 Evaluation of visual fit

Six standard parametric independent models were fitted to each arm; exponential, Weibull, Gompertz, log-logistic, log-normal and the generalised gamma. The model predicted survival times, adjusted background mortality estimated based on life tables published by the Danish Medicines Council (Danish Medicines Council 2024), are displayed in [redacted]. The independent parametric curves all fitted the data and produced good visual predictions for ripretinib and BSC within the observed period.

Figure 21 [redacted]

Abbreviations: BSC: Best supportive care, KM: Kaplan-Meier.

D.1.6 Evaluation of hazard functions

The choice of the [redacted] distribution could not be rejected based on the log cumulative hazard plots ([redacted] and [redacted]).

Figure 22

[redacted]

Abbreviations: KM: Kaplan-Meier.

Figure 23

[redacted]

Abbreviations: KM: Kaplan-Meier.

D.1.7 Validation and discussion of extrapolated curves

The independent parametric curves all fitted the data and produced good visual predictions for ripretinib and BSC within the observed period (see section D.1.5). When fitting curves across two or more treatment groups it is typically recommended to use the same ”type” of model (for example Weibull for the intervention and the control arms) (Latimer 2013). This allows the two-dimensional treatment effect in the shape and scale parameters to differ between treatment arms but prevents the survival hazards from being drastically different between arms. The combined AICs were calculated but were too close to be used to make a judgement for the best statistical fit alone. As such, [redacted] distribution was selected as the base-case curve used for OS extrapolation, as having one of the lowest combined AICs and best visual fit.

D.1.8 Adjustment of background mortality

The model predicted survival times were adjusted for background mortality estimated based on life tables published by the Danish Medicines Council (Danish Medicines Council 2024). These are displayed in [redacted].

D.1.9 Adjustment for treatment switching/cross-over

As per the study design for INVICTUS, study drug treatment was unblinded upon disease progression and patients randomly assigned to placebo were given the option to crossover to receive open-label ripretinib.

As the true survival associated with placebo will be confounded by the benefits of crossover onto open-label ripretinib, conventional survival analysis will underestimate the survival benefit associated with ripretinib. Due to the high proportion of patients who crossed over (30/44 patients; 68%), utilising the results of the ITT analysis for OS in the model was deemed inappropriate as the majority of patients in the placebo arm of the trial received ripretinib. The OS KM curves for ripretinib and BSC from the INVICTUS trial are shown in [redacted] and [redacted], respectively.

Figure 24 [redacted]

Abbreviations: OS: Overall survival, DCO: data cut off.

Figure 25 [redacted]

Abbreviations: OS: Overall survival, DCO: data cut off.

Crossover in the INVICTUS trial occurred following disease progression and was therefore non-random. The NICE Decision Support Unit (DSU) recommends the implementation of a variety of potentially appropriate crossover adjustment approaches when adjusting for this high level of crossover, considering trial characteristics, the switching mechanism, the treatment effect, and data availability. The methods recommended by the DSU include: the two-stage approach, the Inverse Probability of Censoring Weights (IPCW) method, and the Rank Preserving Structural Failure Time Model (RPSFTM) (Latimer NR 2014).

The IPCW method was considered but not used due to the small sample size, and the high proportion of placebo patients crossing over to ripretinib treatment (only 14 placebo patients did not enter the open-label trial period), factors responsible for introducing high levels of error in treatment effect estimates (Latimer NR 2014).

The RPSFTM (rank preserving structural failure time model) method was also considered. This RPSFTM method uses a g-estimation procedure to find the treatment effect, psi. The treatment effect is estimated by balancing counterfactual event times across randomised groups (that is, the time that would have been observed if no treatment were received in either randomised group). A key advantage of the RPSFTM method is that the method is randomisation based, and requires only the randomised treatment groups, the observed event times and treatment history in order to estimate counterfactual survival times (Allison et al. 2017). This method relies on the assumption that the 'common treatment effect' exists – that is, the treatment effect received by switchers must be the same (relative to the time the treatment is taken for) as the treatment effect received by patients initially randomised to the experimental group.

The date of first exposure and date of last exposure to ripretinib for each patient was recorded in the trial and was used in the "rpsftm" package in R to obtain the acceleration

factor and time ratio associated with ripretinib treatment. The possible test options are the log-rank, and the Wald test from a Cox or Weibull regression model. All three options were explored to derive the acceleration factor (Exp[psi]) and time ratio (Exp[-psi]) associated with ripretinib treatment in the ITT population. The log-rank, Cox and Weibull models all outputted time ratios >15 (Table 53). When considering the plotted counterfactual survival times shown in Figure 26, the dissimilarity between the curves indicates the g-estimation did not produce a robust outcome. Table 53 represents the log-rank option but the Cox and Weibull options also outputted very similar results to the log-rank option. Additionally, due to the trial design, whereby patients are only allowed to switch following disease progression, it is unlikely that the "common treatment effect" assumption holds. As such, the RPSFTM method was ruled out as an option to adjust for crossover but has been explored as part of scenario analysis in the CEM.

Table 53 [redacted]

Output	Log-rank	Cox model	Weibull model
Psi (95% CI)	[redacted]	[redacted]	[redacted]
Exp (psi)	[redacted]	[redacted]	[redacted]
Exp (-psi)	[redacted]	[redacted]	[redacted]

Abbreviations: CI: Confidence interval, NA: Not applicable.

Figure 26 [redacted]

[redacted]

The two-stage approach relies on the following assumptions (Latimer NR 2014):

- A secondary baseline can be defined, at which point patients are at risk of crossover (for example progression).
- No unmeasured confounding at the point of the secondary baseline.
- The RCT (INVICTUS) is appropriately randomised up until the point of disease progression.

Two models were explored, one of which included time to progression as a covariate (simple model) and another which included the time to progression, Eastern Cooperative Oncology Group performance status (ECOG), QoL (quality of life) and age as covariates. The following assumptions were made:

- With respect to the time to progression values, 7 of the 44 patients in the placebo group experienced censored progression but continued to be followed up after this. To avoid reducing an already small sample size, it was assumed that the censored time to progression values equated to documented time to progression for these patients.
- ECOG PS and QoL at progression values recorded at the closest time point to progression were used in the analysis.

As time to progression was the only statistically significant covariate and the use of co-variates in the complex model would add additional uncertainty to the analysis, given the small sample size, the simple model was employed in the base-case analysis. Therefore, the complex model was explored in scenario analyses.

The resulting time ratio was then used to "shrink" the post-progression survival times of switching patients to derive a counterfactual dataset unaffected by switching. Censored progression time was assumed to be equal to documented progression time. The base-case analysis was performed with recensoring to guard against informative censoring. Informative censoring occurs when participants are lost to follow-up due to reasons related to the study and can result in biased estimates of treatment effect if not accounted for (Latimer et al. 2019). The resulting median OS times for the base-case analysis (simple model) and complex model are presented in Table 54. The adjusted OS BSC base-case KM curve is shown in Figure 27.

Table 54 [redacted]

Crossover adjustment method	Median OS BSC (weeks)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Abbreviations: BSC: Best supportive care, ECOG PS: Eastern Cooperative Oncology Group performance status, OS: Overall survival, QoL: Quality of life.

Figure 27 [redacted]

Abbreviations: BSC: Best supportive care, DCO: Data cut off, KM: Kaplan-Meier, OS: Overall survival.

D.1.10 Waning effect

D.1.11 Cure-point

D.2 Extrapolation of progression free survival

D.2.1 Data input

Data informing progression free survival is collected in the INVICTUS trial (see Section 6.1.1).

The PFS KM curves for ripretinib and BSC from the INVICTUS trial are shown in and , respectively. Progression was observed within the trial follow-up period in almost all patients in both arms (77.6% and 84.1% for ripretinib and placebo, respectively).

Figure 28

Abbreviations: PFS: Progression-free survival.

Figure 29 [redacted]

Abbreviations: BSC: Best supportive care, PFS: progression-free survival.

D.2.2 Model

Parametric models were fitted directly to the ripretinib + BSC and BSC (placebo) patient-level data to provide long-term extrapolations. Crossover of patients from the placebo to ripretinib in the INVICTUS trial was only allowed following disease progression, therefore crossover correction was not required for the PFS data.

D.2.3 Proportional hazards

Statistical tests were conducted to test if the proportional hazards (PH) assumption holds between the two treatment arms of INVICTUS within the observed trial follow-up period. Two statistical tests were conducted: the complementary log-log plot and the Schoenfeld residuals test. The outcomes of these statistical tests were used to determine whether the null hypothesis, that PH between treatment arms holds, could be rejected.

[redacted]

[redacted]

Figure 30 [redacted]

Abbreviations: BSC: Best supportive care.

Figure 31 [redacted]

[redacted] standard parametric independent models were fitted to each arm of the study data.

D.2.4 Evaluation of statistical fit (AIC and BIC)

A summary of the goodness-of-fit statistics for the PFS extrapolations is presented in [redacted].

Table 55 [redacted]

Distribution	Ripretinib		BSC		Combined	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	[redacted]					
Weibull	[redacted]					
Gompertz	[redacted]					
Log-logistic	[redacted]					
Log-normal	[redacted]					
Generalised gamma	[redacted]					

Abbreviations: AIC: Akaike information criterion, BIC: Bayesian information criterion, BSC: Best supportive care.

The [redacted] distribution was selected as the base-case curve used for PFS extrapolation, based on having one of the lowest combined AICs and best visual fit (see section D.2.5).

D.2.5 Evaluation of visual fit

Six standard parametric independent models were fitted to each arm of the study data; exponential, Weibull, Gompertz, log-logistic, log-normal and the generalised gamma ([redacted]).

Figure 32 [redacted]

[redacted]

Abbreviations: BSC: Best supportive care, KM: Kaplan-Meier, PFS: Progression-free survival.

The independent parametric curves all fitted the data and produced good visual predictions for ripretinib and BSC within the observed period.

D.2.6 Evaluation of hazard functions

The choice of the [redacted] distribution could not be rejected based on the log cumulative hazard plots ([redacted] and [redacted]).

Figure 33

[redacted]

Abbreviations: KM: Kaplan-Meier.

Figure 34

[redacted]

Abbreviations: BSC: Best supportive care, KM: Kaplan-Meier.

D.2.7 Validation and discussion of extrapolated curves

Given the maturity of the progression free survival endpoint (77.6% and 84.1% progression for ripretinib and placebo, respectively), the independent parametric curves all fitted the data and produced good visual predictions for ripretinib and BSC within the observed period. When fitting curves across two or more treatment groups it is typically recommended to use the same ”type” of model (for example Weibull for the intervention and the control arms). This allows the two-dimensional treatment effect in the shape and scale parameters to differ between treatment arms but prevents the survival hazards from being significantly different between arms. The combined AICs were calculated but were too close to be used to make a judgement for the best statistical fit alone. As such, the [redacted] distribution was selected as the base-case curve used for PFS extrapolation, based on having one of the lowest combined AICs and best visual fit.

D.2.8 Adjustment of background mortality

[redacted]

D.2.9 Adjustment for treatment switching/cross-over

[redacted]

D.2.10 Waning effect

[redacted]

D.2.11 Cure-point

[redacted]

D.3 Extrapolation of time to treatment discontinuation

D.3.1 Data input

The parametric survival models to divide the PD state into on treatment and off treatment were based on an analysis of a composite endpoint of PFS and treatment discontinuation defined as follows:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- [redacted]

The KM curves of this composite endpoint are presented alongside the OS and PFS endpoints in [redacted].

Figure 35

[redacted]

Abbreviations: PFS: Progression free survival.

D.3.2 Model

Seven standard parametric independent models were fitted to the study data: Exponential, Weibull, Gompertz, log-logistic, log-normal, gamma, generalised gamma.

D.3.3 Proportional hazards

[redacted].

D.3.4 Evaluation of statistical fit (AIC and BIC)

A summary of the goodness-of-fit statistics for the composite PFS and discontinuation endpoint extrapolations is presented in Table 56. The [redacted] model was selected as the default on the basis that it had the lowest AIC and BIC of the seven models.

Table 56 AIC and BIC statistical goodness-of-fit data for composite of PFS and discontinuation of ripretinib (any dose)

Distribution	Ripretinib	
	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion, BIC: Bayesian information criterion, PFS: Progression free survival.

D.3.5 Evaluation of visual fit

Seven standard parametric independent models were fitted to the study data: exponential, Weibull, Gompertz, log-logistic, log-normal, gamma and generalised gamma. These models are visualised in [redacted].

Figure 36

[redacted]

Abbreviations: AIC: Akaike information criterion, BIC: Bayesian information criterion, LL; lower limits.

D.3.6 Evaluation of hazard functions

[redacted].

D.3.7 Validation and discussion of extrapolated curves

[redacted] fitted the data and produced good visual predictions for ripretinib within the observed period. The [redacted] model was selected as the default on the basis that it had the lowest AIC and BIC of the seven models.

D.3.8 Adjustment of background mortality

[redacted].

D.3.9 Adjustment for treatment switching/cross-over

[redacted].

D.3.10 Waning effect

[redacted].

D.3.11 Cure-point

[redacted].

Appendix E. Serious adverse events

[redacted].

[redacted]:

- [redacted]
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- [redacted]
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Appendix F. Health-related quality of life

Below follows a summary of EQ-5D domains of importance for advanced GIST patients as well as data from the disease-specific instrument.

Among all cancer patients, the measurement properties of these instruments have been investigated. Differences of approximately 10 points in EORTC QLQ-C30 individual items and scale scores (range: 0 to 100, with higher scores on function scales reflecting better function and higher scores on symptom scales reflecting increased symptoms), approximately 7 to 12 points in EQ-VAS scores (range: 0 to 100, with 0 and 100 representing “worst imaginable health” and ”best imaginable health,” respectively), and approximately 0.07 to 0.12 (using the UK algorithm) in EQ-5D-5L utility index scores (range: < 0 to 1, with 0 and 1 representing the health states “dead” and ”perfect health,” respectively) are typically considered significant. MICDs for EQ-5D-5L descriptive system dimension scores (range: 1 to 5, representing no problems, slight problems, moderate problems, severe problems, and extreme problems, respectively) are uncertain.

F.1 EQ-5D-5L specific domains

Below follows the proportions of participants reporting for the domain specific findings from the EQ-5D-5L instrument from the INVICTUS trial at baseline and C2D1 with the May 31 2019 data cut.

Table 57: EQ-5D-5L scores for all domains at baseline and C2D1 [ITT population, May 31, 2019 data cut]

	Ripretinib 150 mg QD	Placebo
	n = 85	n = 44
Mobility		
Baseline		
1	41 (48.2)	25 (56.8)
2	18 (21.2)	8 (18.2)
3	12 (14.1)	6 (13.6)
4	2 (2.4)	2 (4.5)
5	1 (1.2)	1 (2.3)
C2D1		
Patients, n	79	33

1	40 (50.6)	16 (48.5)
2	27 (34.2)	12 (36.4)
3	10 (12.7)	4 (12.1)
4	2 (2.5)	1 (3.0)
Self-care		
Baseline		
1	63 (74.1)	36 (81.8)
2	9 (10.6)	3 (6.8)
3	2 (2.4)	1 (2.3)
4	0	1 (2.3)
5	0	1 (2.3)
C2D1		
Patients, n	79	33
1	70 (88.6)	30 (90.9)
2	8 (10.1)	2 (6.1)
3	1 (1.3)	1 (3.0)
Usual activities		
Baseline		
1	30 (35.3)	21 (47.7)
2	25 (29.4)	10 (22.7)
3	14 (16.5)	8 (18.2)
4	5 (5.9)	2 (4.5)
5	0	1 (2.3)
C2D1		
Patients, n	79	33
1	42 (53.2)	14 (42.4)
2	25 (31.6)	13 (39.4)

3	10 (12.7)	4 (12.1)
4	1 (1.3)	2 (6.1)
5	1 (1.3)	0
Pain/discomfort		
Baseline		
1	18 (21.2)	10 (22.7)
2	36 (42.4)	18 (40.9)
3	14 (16.5)	9 (20.5)
4	6 (7.1)	4 (9.1)
5	0	1 (2.3)
C2D1		
Patients, n	78	33
1	18 (23.1)	9 (27.3)
2	36 (46.2)	11 (33.3)
3	20 (25.6)	9 (27.3)
4	3 (3.8)	4 (12.1)
5	1 (1.3)	0
Anxiety/depression		
Baseline		
1	35 (41.2)	18 (40.9)
2	25 (29.4)	15 (34.1)
3	11 (12.9)	8 (18.2)
4	2 (2.4)	1 (2.3)
5	1 (1.2)	0
C2D1		
Patients, n	78	33
1	40 (51.3)	14 (42.4)

2	21 (26.9)	14 (42.4)
3	15 (19.2)	1 (3.0)
4	2 (2.6)	3 (9.1)
5	0	1 (3.0)

Data is reported as n (%) unless otherwise indicated.
Each dimension of the EQ-5D-5L has 5 levels: no problems (1), slight problems (2), moderate problems (3), severe problems (4), and extreme problems (5). The digits for the 5 dimensions can be combined into a 5-digit number that describes the patient's health state.
There were 13 patients with missing information at baseline (11 in the ripretinib arm and 2 in the placebo arm).
Abbreviations: C: cycle, D: day, EQ-5D-5L:EuroQoL 5-Dimension 5-Level, QD: once daily.
Source: (Schöffski et al. 2022)

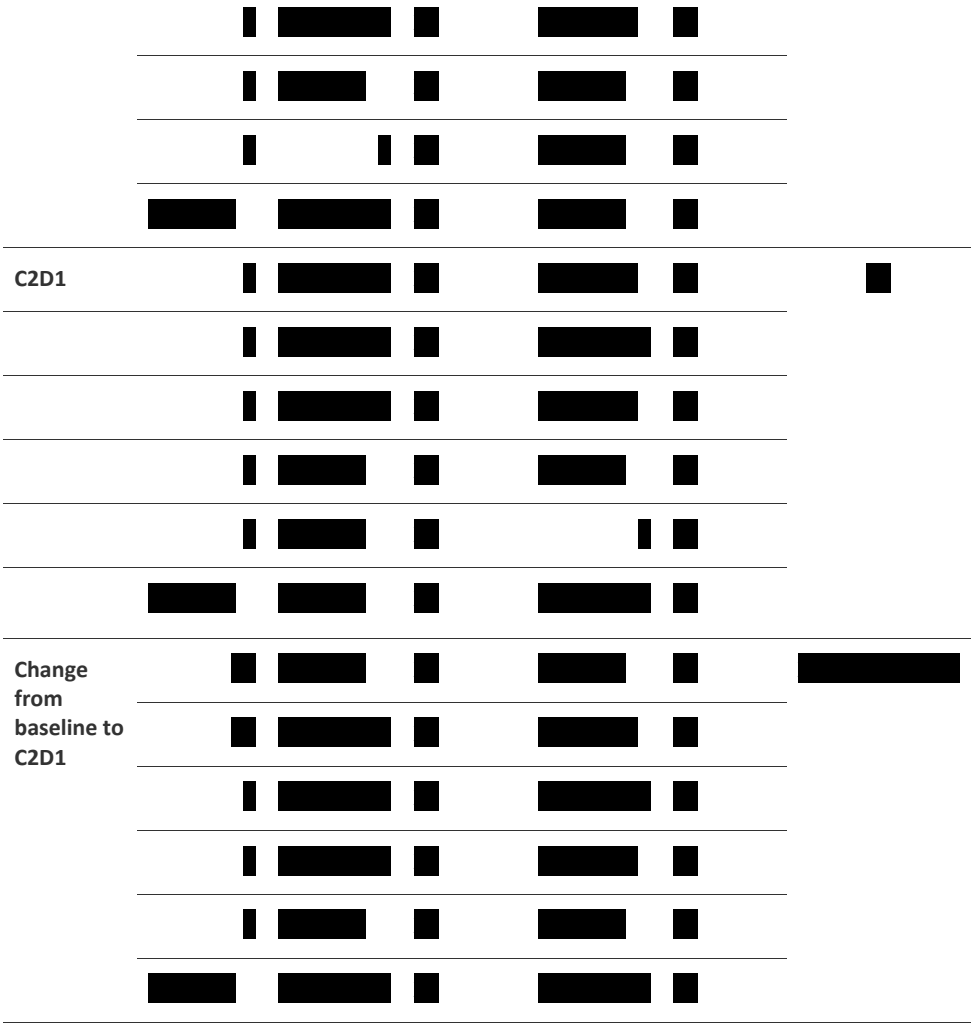
Change from baseline was calculated for the domains of pain/discomfort (Table 58) and usual activities (Table 59).Below follows the proportions of participants reporting for the domain specific findings from the EQ-5D-5L instrument from the INVICTUS trial at baseline and C2D1 with the May 31 2019 data cut, namely the [redacted]

[redacted]

Table 58: HRQoL EQ-5D-5L pain/discomfort summary statistics [ITT population - Change from Baseline to Cycle 2 Day 1 in Double-Blind Treatment Period, May 31, 2019 data cut]

	Categories	Intervention (Ripretinib)		Comparator (Placebo)		Intervention vs. comparator
Pain and discomfort		N (%)	Mean (SE)	N (%)	Mean (SE)	Difference (95% CI) p-value
Baseline	[redacted]					

[redacted]

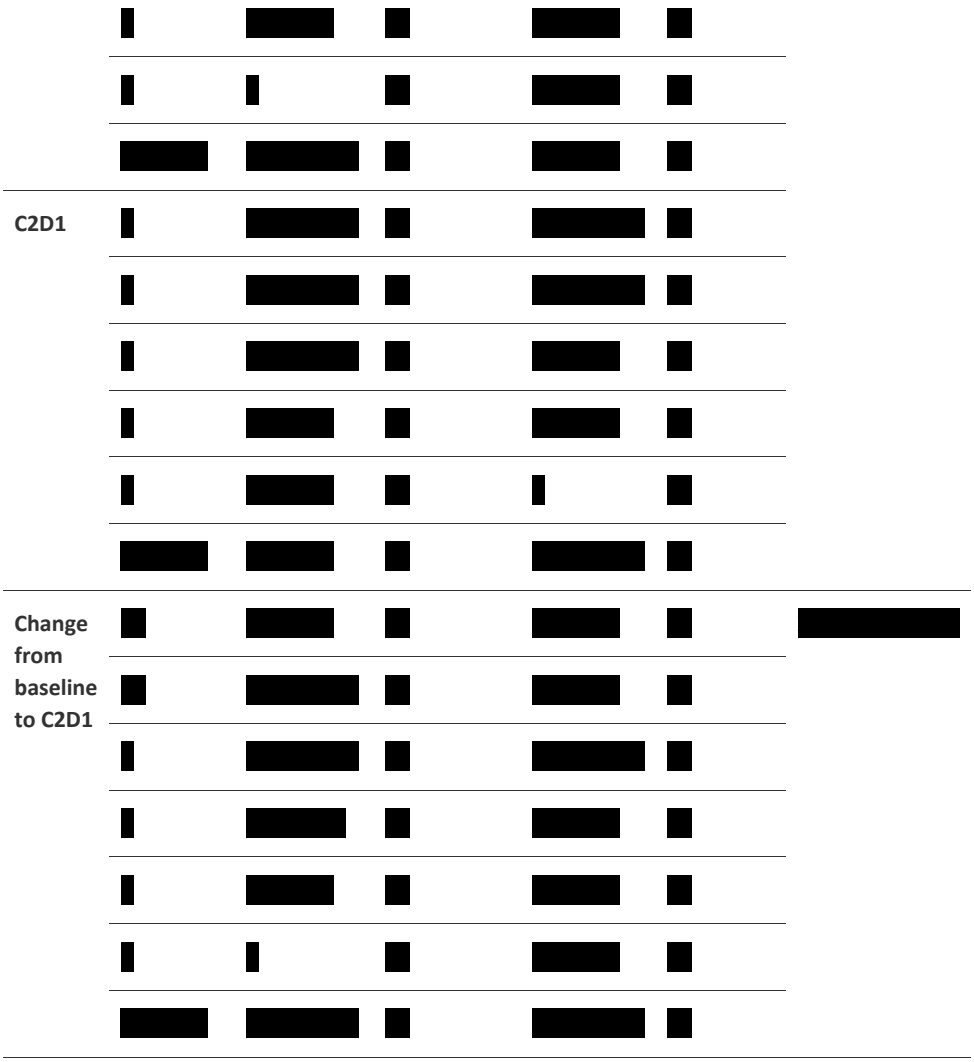


C2D1					
Change from baseline to C2D1					

Cochran–Mantel–Haenszel test was used to test the change in response scale at Day 1 of Cycle 2 from baseline between the ripretinib and placebo arms and derive the p-value
Abbreviations: CI: Confidence interval; C2D1: Day one of cycle 2; NR: Not reported; SE: Standard error.
Source: [redacted]

Table 59: HRQoL EQ-5D-5L usual activities summary statistics [ITT population - Change from Baseline to Cycle 2 Day 1 in Double-Blind Treatment Period, May 31, 2019 data cut]

Categories		Intervention (Ripretinib n=85)	Comparator (Placebo n=44)		Intervention vs. comparator
Usual activities	N (%)	Mean (SE)	N (%)	Mean (SE)	Difference (95% CI) p-value
Baseline					



Cochran–Mantel–Haenszel test was used to test the change in response scale at Day 1 of Cycle 2 from baseline between the ripretinib and placebo arms and derive the p-value
Abbreviations: CI: Confidence interval; C2D1: Day one of cycle 2; NA: Not applicable; NR: Not reported; SE: Standard error.
Source: [redacted]

F.2 Disease-specific HRQoL instrument: EORTC-QLQ-C30

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-item (EORTC-QLQ-C30) is a disease-specific instrument consisting of a total of 30 questions, divided into the symptom scales assigned to morbidity as well as the functional scales relevant to assessing HRQoL and global health status specifically for patients with cancer. On all scales, a higher value corresponds to higher agreement. Accordingly, an increase in the scale value of the symptom scales represents a worsening of the symptoms. The evaluation takes place in two steps. The first step is to calculate the average of the items contributing to the scale. This is the raw score for the scale. After the raw score is calculated, the second step is to perform a linear regression to standardise the raw scores so that the scale score ranges from 0 to 100. The higher

value represents a higher QoL in disease-related symptoms. For QoL, ”minimal clinically important difference” (MCID) values are established as 0.5 times the standard deviation (Norman et al. 2003). These measures are an extremely important summary of the patient's self-perception and the influence of their illness as well as the chosen therapy on their state of health. The physical functioning and role functioning scales are two of the PROs identified by the US Food and Drug Administration as existing tools that measure core PROs that are clinically relevant and important to patients (Schöffski et al. 2022). The change from baseline at cycle 2, day 1 (C2D1) for the physical function, role function, overall health and overall quality of life scores from the EORTC QLQ-30 are summarised in below Figure 37.

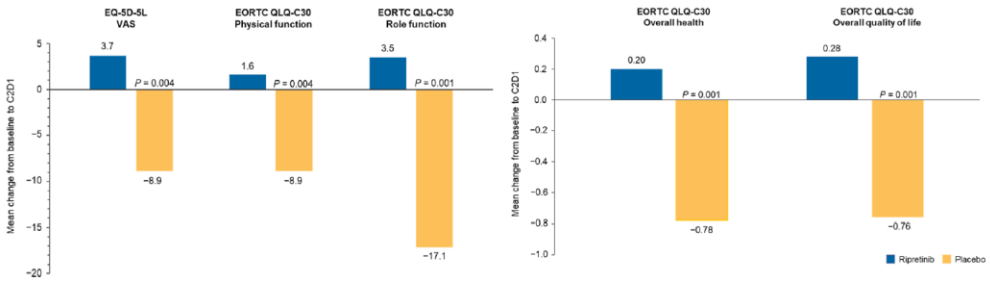


Figure 37: Change from baseline to cycle 2, day 1 in EORTC QLQ-C30 measures and EQ-VAS [ITT population, May 31, 2019 data cut]

Mean change from baseline to C2D1 in the EQ-5D-5 L VAS (A), EORTC QLQ-C30 physical function (A), EORTC QLQ-C30 role function (A), EORTC QLQ-C30 overall health (B), and EORTC QLQ-C30 quality of life (B). 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. C2D1, cycle 2, day 1; EORTC QLQ-C30, European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5 L, EuroQoL 5-Dimension 5-Level; VAS, visual analogue scale
Source: (Schöffski et al. 2022)

Here follows a summary of the efficacy of ripretinib in disease-specific domains as well as the overall physical and role functioning scores based on EORTC QLQ-C30 in the primary analysis data cut May 15, 2019 for the ITT population. Owing to the hierarchical testing and that ORR narrowly missed statistical significance, HRQoL differences by treatment were not formally tested statistically. Changes in HRQoL as determined by changes from baseline to C2D1 in physical and role functioning scale subsets of the EORTC-QLQ-C30. Analysis of covariance models were built to assess for change from baseline to C2D1. Fixed effects were treatment, ECOG performance status at baseline, and the number of previous treatments. A patient was excluded from the analyses if data from baseline or C2D1 were missing.

Table 60 contains the mean change from baseline for the trial arms across the domains as well as for the overall physical and role functioning scores.

Table 60:EORTC QLQ-C30 change from baseline to C2D1

	Ripretinib 150 mg QD n = 85 mean (SD)	Placebo n = 44 mean (SD)
Emotional functioning		
Baseline	70.5 (22.5)	71.2 (23.51)

C2D1	76.5 (19.56)	73.0 (23.94)
Change from baseline	5.1 (16.74)	−2.6 (21.53)
Cognitive functioning		
Baseline	80.4 (21.78)	79.8 (21.63)
C2D1	84.2 (18.85)	77.3 (26.29)
Change from baseline	2.1 (17.93)	−9.4 (23.16)
Social functioning		
Baseline	70.5 (28.74)	67.9 (30.22)
C2D1	78.9 (23.68)	72.7 (29.41)
Change from baseline	6.2 (24.27)	−4.7 (29.70)
Fatigue symptoms		
Baseline	61.0 (27.29)	60.6 (29.47)
C2D1	62.3 (24.03)	54.5 (28.38)
Change from baseline	−1.3 (25.49)	−13.2 (25.62)
Nausea/vomiting symptoms		
Baseline	89.2 (19.20)	90.5 (18.09)
C2D1	88.8 (13.54)	87.4 (25.01)
Change from baseline	−2.9 (17.49)	−4.7 (31.46)
Pain symptoms		
Baseline	65.8 (29.31)	71.4 (28.82)
C2D1	70.3 (23.67)	65.2 (32.64)
Change from baseline	1.0 (27.64)	−10.4 (31.32)
Dyspnoea symptoms		
Baseline	81.1 (21.43)	78.6 (27.37)
C2D1	79.3 (23.45)	82.8 (25.17)
Change from baseline	−3.8 (22.37)	−2.1 (25.31)
Insomnia symptoms		
Baseline	68.5 (32.59)	72.2 (32.02)
C2D1	68.8 (28.42)	63.6 (33.71)
Change from baseline	−1.9 (32.54)	−8.3 (32.79)
Appetite loss symptoms		
Baseline	73.9 (31.34)	69.8 (37.40)
C2D1	78.1 (23.80)	67.7 (35.83)
Change from baseline	1.0 (27.20)	−8.3 (36.91)
Constipation symptoms		
Baseline	77.5 (27.09)	80.2 (25.57)
C2D1	75.1 (29.94)	74.7 (32.31)
Change from baseline	−4.3 (34.01)	−6.3 (26.01)

Diarrhoea symptoms		
Baseline	91.4 (15.66)	87.3 (22.03)
C2D1	93.7 (15.17)	86.9 (29.98)
Change from baseline	1.4 (18.33)	−2.1 (25.31)
Financial difficulty symptoms		
Baseline	73.0 (31.05)	69.0 (34.05)
C2D1	80.6 (25.93)	70.7 (32.01)
Change from baseline	5.2 (25.15)	−3.1 (19.60)
Role Functioning		
Baseline	[redacted]	[redacted]
C2D1	[redacted]	[redacted]
Change from baseline	3.5 (SE [redacted])	-17.1 (SE [redacted])
Physical Functioning		
Baseline	[redacted]	[redacted]
C2D1	[redacted]	[redacted]
Change from baseline	1.6 (SE [redacted])	-8.9 (SE [redacted])

Abbreviations: C2D1: Day 1 in Cycle 2, EORTC-QLQ-C30: European Organization for Research and Treatment of Cancer Questionnaire, HRQoL: Health-related quality of life, QD: Quaque die, once daily, SD: Standard deviation, SE: Standard error.
Note: For change in Role functioning and Physical Functioning, the adjusted mean, standard error, confidence interval, and p-value are estimated from an ANCOVA model that included factors for study treatment, number of prior anticancer treatment, and ECOG status at baseline as fixed effects.
Source: (Schöffski et al. 2022), supplemented with data on file (Deciphera 2019)

Patients in the ripretinib group reported improvement in the physical and role functioning domains (See Table 61 for further details). The difference between those who received ripretinib and placebo was considered clinically significant (Blay et al. 2020). Role and physical functioning from baseline to cycle 2 day 1 remained stable in the ripretinib group with adjusted mean change in score of 3.5 (95% CI: –3.4 to 10.5) for role functioning and 1.6 (–2.5 to 5.7) for physical functioning, compared with a decrease with placebo of 17.1 for role functioning (95% CI: –27.0 to –7.1) and a decrease of 8.9 for physical functioning (–14.8 to –3.0) (Blay et al. 2020). Owing to hierarchal testing procedures of the endpoints, the QoL endpoint could not be formally tested for statistical significance. The differences between treatment arms were all greater than the corresponding MCID and thus clinically significant. A similar trend was observed in the "overall health" and "overall quality of life" domains.

Furthermore, the analysis showed that the QoL scores of patients in the ripretinib group remained stable over time (Schöffski et al. 2022). Changes in scores were measured from baseline and over time in the ripretinib group, with stabilisation in scores for all measures from cycle 1 to cycle 10, which indicates that these patients were able to maintain their QoL and functionality (Schöffski et al. 2022). The most common treatment-emergent adverse event (TEAE) with ripretinib was alopecia, however, QoL was also maintained up to treatment cycle 10, day 1 in patients receiving ripretinib who developed alopecia

(Schöffski et al. 2022). Patients in the placebo group reported definitive deterioration in their health within a median of 8 weeks, while the median time to definitive deterioration was not reached in the ripretinib group.

As such, ripretinib was observed to confer a clinically significant improvement in HRQoL as compared with placebo as defined by the MCID, with this effect remaining stable for the duration of the study period.

Table 61: Disease specific HRQoL INVICTUS data

Outcome	Study arm	N	Result (CI)	Estimated absolute difference in effect	Description of methods used for estimation
EORTC QLQ-C30 (physical functioning) **Change from baseline to cycle 2 day 1** **[DCO 31 May 2019]**	Ripretinib	85	1.6 (–2.5 to 5.7)	10.5; p-value: 0.004	ITT population. Analysis of covariance models were built to assess for change from baseline to cycle 2 day 1 for the EORTC QLQ-C30 scales. Fixed effects were treatment, ECOG performance status at baseline, and the number of previous treatments. A patient was excluded from the analyses if data from baseline or C2D1 were missing. Numbers included for EORTC QLQ-C30 (physical functioning) in analysis were: At baseline: Ripretinib: 75.7 (n=74, SD=21.6, 95%CI=70.7-80.7); Placebo: 76.0 (n=42, SD=26.5, 95%CI=67.8-84.3) At C2D1: Ripretinib: 79.4 (n=80, SD=17.3, 95%CI=75.5-83.3); Placebo: 75.2 (n=33, SD=20.2, 95%CI=68.0-82.3)
	Placebo	44	-8.9 (–14.8 to –3.0)		
EORTC QLQ-C30 (role functioning) **Change from baseline to cycle 2 day 1** **[DCO 31 May 2019]**	Ripretinib	85	3.5 (–3.4 to 10.5)	20.6; p-value: 0.001	Numbers included for EORTC QLQ-C30 (role functioning) in analysis were: At baseline: Ripretinib: 69.4 (n=74, SD=30.1, 95% CI=62.4-76.3); Placebo: 73.8 (n=42, SD=30.4, 95% CI= 64.3-83.3) At C2D1: Ripretinib: 75.1 (n=79, SD=26.1, 95% CI=69.3-81.0); Placebo: 65.2 (n=33, SD=27.8, 95% CI=55.3-75.0)
	Placebo	44	-17.1 (–27.0 to –7.1)		

Abbreviatons: CI: Confidence interval; C2D1: Day one of cycle 2; DCO: Data cut off; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Questionnaire; HRQoL: Health related quality of life; SD: Standard deviation.
Source: (Blay et al. 2020).

Appendix G. Probabilistic sensitivity analyses

Parameters used in the probabilistic sensitivity analysis are shown in Table 62.

Table 62 Overview of parameters in the probabilistic sensitivity analysis (PSA)

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Cohort inputs				
Percentage male	[redacted]	[redacted]	[redacted]	[redacted]
Efficacy parameters				
Ripretinib – PFS – Log Normal distribution – constant (coefficient)	[redacted]	[redacted]	[redacted]	[redacted]
Ripretinib – PFS – Log Normal distribution – ln_sig (coefficient)	[redacted]	[redacted]	[redacted]	[redacted]
BSC – PFS – Log Normal distribution – constant (coefficient)	[redacted]	[redacted]	[redacted]	[redacted]
BSC – PFS – Log Normal distribution – ln_sig (coefficient)	[redacted]	[redacted]	[redacted]	[redacted]
Ripretinib – OS – Log Normal distribution – constant (coefficient)	[redacted]	[redacted]	[redacted]	[redacted]
Ripretinib – OS – Log Normal distribution – ln_sig (coefficient)	[redacted]	[redacted]	[redacted]	[redacted]
BSC – OS – Log Normal distribution – constant (coefficient)	[redacted]	[redacted]	[redacted]	[redacted]
BSC – OS – Log Normal distribution – ln_sig (coefficient)	[redacted]	[redacted]	[redacted]	[redacted]
Utility parameters				
State PF	[redacted]	[redacted]	[redacted]	[redacted]
State PD On	[redacted]	[redacted]	[redacted]	[redacted]

State PD Off	[redacted]	[redacted]	[redacted]	[redacted]
State PD (BSC)	[redacted]	[redacted]	[redacted]	[redacted]
Ripretinib adverse event total disutility	[redacted]	[redacted]	[redacted]	[redacted]
BSC adverse event total disutility	[redacted]	[redacted]	[redacted]	[redacted]
Cost parameters				
Ripretinib pre-treatment cost (DKK)	[redacted]	[redacted]	[redacted]	[redacted]
Ripretinib relative dose intensity	[redacted]	[redacted]	[redacted]	[redacted]
BSC cost per cycle (ripretinib arm) PDOn (DKK)	[redacted]	[redacted]	[redacted]	[redacted]
BSC cost per cycle (ripretinib arm) PDOff (DKK)	[redacted]	[redacted]	[redacted]	[redacted]
BSC cost per cycle (ripretinib arm) PF (DKK)	[redacted]	[redacted]	[redacted]	[redacted]
BSC cost per cycle PF (DKK)	[redacted]	[redacted]	[redacted]	[redacted]
BSC cost per cycle PD (DKK)	[redacted]	[redacted]	[redacted]	[redacted]
BSC relative dose intensity	[redacted]	[redacted]	[redacted]	[redacted]
Ripretinib PF health state total cost (DKK)	[redacted]	[redacted]	[redacted]	[redacted]
Ripretinib PDOff health state total cost (DKK)	[redacted]	[redacted]	[redacted]	[redacted]
Ripretinib PDOn health state total cost (DKK)	[redacted]	[redacted]	[redacted]	[redacted]
BSC PF health state total cost (DKK)	[redacted]	[redacted]	[redacted]	[redacted]
BSC PD health state total cost (DKK)	[redacted]	[redacted]	[redacted]	[redacted]
Ripretinib palliative care cost PF (DKK)	[redacted]	[redacted]	[redacted]	[redacted]

Ripretinib palliative care cost PD (DKK)	[redacted]	[redacted]	[redacted]	[redacted]
BSC palliative care cost PF (DKK)	[redacted]	[redacted]	[redacted]	[redacted]
BSC palliative care cost PD (DKK)	[redacted]	[redacted]	[redacted]	[redacted]
End of life cost (DKK)	[redacted]	[redacted]	[redacted]	[redacted]
Ripretinib adverse event total cost (DKK)	[redacted]	[redacted]	[redacted]	[redacted]
BSC adverse event total cost (DKK)	[redacted]	[redacted]	[redacted]	[redacted]
Ripretinib PF transportation & patient time total cost (DKK)	[redacted]	[redacted]	[redacted]	[redacted]
Ripretinib PDOff transportation & patient time total cost (DKK)	[redacted]	[redacted]	[redacted]	[redacted]
Ripretinib PDOn transportation & patient time total cost (DKK)	[redacted]	[redacted]	[redacted]	[redacted]
BSC PF transportation & patient time total cost (DKK)	[redacted]	[redacted]	[redacted]	[redacted]
BSC PD transportation & patient time total cost (DKK)	[redacted]	[redacted]	[redacted]	[redacted]
Ripretinib pre-treatment transportation & patient time cost (DKK)	[redacted]	[redacted]	[redacted]	[redacted]

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

A thorough SLR was conducted to ensure a complete and updated understanding of the drug (ripretinib) for clinical assessment in terms of efficacy and safety for advanced GIST patients. The process followed established practice and was comprised of the following core stages: definition of scope and agreement of search terms, implementation of searches and abstract review to inform included papers, and extraction and quality assessment of data.

The scope of the SLR was defined in terms of criteria such as the Patient population, the Intervention, the Comparators, the Outcomes measures, and the Study design (PICOS Statement) as described in Table 63 below.

Table 63 PICOS statement for the clinical SLR in metastatic GIST

Clinical SLR PICOS	
Patient population	Patients diagnosed with advanced/metastatic or unresectable gastrointestinal stromal tumours (GIST) receiving fourth-line (4L) therapy
Intervention and Comparators	**Intervention** Ripretinib (DCC-2618) **Comparators** Imatinib (Gleevec, Glivec, STI571), Regorafenib (Stivarga, Bay 73-4506), Sunitinib (Sutent, SU011248)) Other interventions studied for ≥4L GIST BSC
Outcomes measures	Overall survival (OS) Progression-free survival (PFS), disease-free survival, event-free survival Response rate Duration of response, time to response Other efficacy endpoints Any safety endpoints

	Quality of life/Patient-reported outcomes (PROs)
Study design	Randomised clinical trials (including extension studies) Single arm prospective interventional studies Sub-group analyses of previously published studies Systematic reviews and meta-analyses (for cross-checking only) Pooled analyses (for cross-checking only)

Abbreviations: GIST: Gastrointestinal stromal tumours, OS: Overall survival, PFS: Progression-free survival, PROs: Patient-reported outcomes, 4L: Fourth line.

The key biomedical literature databases (Medical Literature Analysis and Retrieval System Online [MEDLINE®], Excerpta Medica Database [Embase®]) and Cochrane collaboration were consulted as described in Table 64 below. This is in accordance with the list of databases suggested by the HTA organisations, such as the CADTH (Canada) and NICE (England and Wales). MEDLINE® was searched also for Epub Ahead of Print, In-Process, and other non-indexed citations to ensure that information from non-indexed citations would also be retrieved.

Table 64 Bibliographic databases included in the clinical literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Ovid	2000-present	08.04.2024
Medline	Ovid	2000-present	08.04.2024
Cochrane	Ovid	2000-present	08.04.2024

Other sources were used to enrich the search. The bibliographies of systematic reviews and meta-analyses identified through database searches were used to identify key studies. Furthermore, bibliographies from selected studies were reviewed to identify studies relevant to the SLR. This process ensured that papers and articles not picked up in the initial search were included in the review.

In addition, the websites of the regulatory and HTA authorities in countries of particular interest were consulted, which included the UK (England and Scotland), Australia, and Canada: NICE - National Institute for Health and Care Excellence, SMC - Scottish Medicines Consortium, PBAC - Pharmaceutical Benefits Advisory Committee, CADTH - Canadian Agency for Drugs and Technologies in Health. The selected countries represent larger reimbursement markets in Europe, Australia, and North America and provide the most robust resources for the identification of relevant documents. These other sources are detailed in Table 65 below.

Table 65 Other sources included in the clinical literature search

Source name	Location/source	Search strategy	Date of search

Bibliographies	Systematic reviews and meta-analyses found through database searches	Review of all systematic review and meta-analysis bibliographies.	Final search conducted in April 2024
NICE	www.nice.org.uk	Searches for relevant literature using key words in website-based search function.	Final search conducted in April 2024
SMC	www.scottishmedicines.org.uk	Searches for relevant literature using key words in website-based search function.	Final search conducted in April 2024
PBAC	www.pbac.pbs.gov.au	Searches for relevant literature using key words in website-based search function.	Final search conducted in April 2024
CADTH	www.cadth.ca	Searches for relevant literature using key words in website-based search function.	Final search conducted in April 2024
Clinical trials	www.clinicaltrials.gov	Searches for relevant literature using key words in website-based search function.	Final search conducted in April 2024

Conference abstracts were searched from 2017 to 2024 to retrieve the latest studies, using the search terms: “GIST”, “Gastrointestinal stromal tumor”, and “Gastrointestinal stromal tumour”. The conference proceedings of the following organisations were searched manually for abstracts: ASCO (2018-2023), ASCO GI (2018-2024), and ESMO (2017-2023). This is detailed in Table 66 below.

Table 66 Conference material included in the clinical literature search

Conference	Source of abstracts	Search strategy	Words/Terms searched	Date of search
American Society of Clinical Oncology (ASCO)	Conference proceedings	Manual search (2018-2023)	"GIST”, “Gastrointestinal stromal tumour”, and “Gastrointestinal stromal tumour”	April 2024
American Society of Clinical Oncology Gastrointestinal Symposium (ASCO GI)	Conference proceedings	Manual search (2018-2024)	“GIST”, “Gastrointestinal stromal tumour”, and “Gastrointestinal stromal tumour”	April 2024

European Society for Medical Oncology (ESMO)	Conference proceedings	Manual search (2017-2023)	"GIST", "Gastrointestinal stromal tumour", and "Gastrointestinal stromal tumour"	April 2024

H.1.1 Search strategies

The Ovid platform was used to conduct searches in the mentioned literature databases. Ovid is a search platform that provides standardised access to a wide range of clinical literature databases and is an accepted tool by HTA agencies for conducting SLRs. Data were obtained by combining extensive lists of search terms for the indication, interventions, and study designs. Results were cross-checked against utility/disutility-containing publications identified from the clinical and economic SLR to ensure the completeness of the evidence. The search strings included in the literature search are detailed in Table 67, Table 68, and Table 69 below.

Table 67 Search strategy table for Medline in the clinical SLR

No.	Query	Results
#1	Gastrointestinal Stromal Tumors/	17677
#2	Neoplasm Metastasis/	318305
#3	Recurrence/	414373
#4	exp Randomized Controlled Trial/ or exp Random Allocation/ or exp randomization/	1617894
#5	exp placebos/	477809
#6	exp Double-Blind Method/ or exp Single-Blind Method/	676575
#7	exp clinical trial/ or exp clinical trial, phase ii/ or exp clinical trial, phase iii/ or exp controlled clinical trial/	2886002
#8	exp controlled clinical trials as topic/ or exp Randomized Controlled Trials as Topic/ or exp clinical trials as topic/	939826
#9	exp Multicenter Study/	733259
#10	exp Meta-Analysis/ or exp Meta-Analysis as Topic/ or exp "Systematic Review"/	1006572

Table 68 Search strategy table for Embase in the clinical SLR

No.	Query	Results
#1	gastrointestinal stromal tumor/	30038
#2	metastasis/ or advanced cancer/	611891
#3	cancer recurrence/ OR relapse/ OR recurrent disease/	848075
#4	exp Randomized Controlled Trial/ or exp Random Allocation/ or exp randomization/	1617894
#5	exp placebo/	411093
#6	exp double blind procedure/ or exp single blind procedure/ or exp crossover procedure/	318966
#7	exp clinical trial/ or exp phase 2 clinical trial/ or exp phase 3 clinical trial/ or exp controlled clinical trial/	2886002
#8	exp "controlled clinical trial (topic)"/ or exp "clinical trial (topic)"/ or exp "randomized controlled trial (topic)"/	460018
#9	exp multicenter Study/	733259
#10	exp meta analysis/ or exp "meta analysis (topic)"/ or exp "systematic review"/	982481

Table 69 Search strategy table for all databases in the clinical SLR

No.	Query	Results
#1	(gastrointestinal stromal tumor$ or gastro-intestinal stromal tumor$ or gastro intestinal stromal tumor$ or gastrointestinal stromal tumour$ or gastro-intestinal stromal tumour$ or gastro intestinal stromal tumour$).ti,ab.	28482
#2	(gastrointestinal stromal neoplasm$ or gastro-intestinal stromal neoplasm$ or gastro intestinal stromal neoplasm$).ti,ab.	11
#3	(gastrointestinal stromal sarcoma$ or gastro-intestinal stromal sarcoma$ or gastro intestinal stromal sarcoma$).ti,ab.	39
#4	GIST.ti,ab.	23414
#5	(metasta$ or advanced or unresectable or un-resectable or non-resectable or nonresectable).ti,ab.	2973221
#6	(relap$ OR refract$ OR resist$ OR persist$ OR return$ OR reoccur$ OR reocur$ OR (re adj2 occur) OR (re adj2 ocur$) OR recurren$ OR salvage$).ti,ab.	7823693

No.	Query	Results
#7	(prior or progress$ or (previous$ adj3 treat$) or (previous$ adj3 receiv$) or pretreat$ or fail$ or unrespon$).ti,ab.	9215750
#8	(imatinib or sunitinib or regorafenib).ti,ab.	69248
#9	clinical trials as topic.sh.	242993
#10	randomized controlled trial.pt.	610379
#11	controlled clinical trial.pt.	95518
#12	random$.ti,ab,kw,sh.	5463530
#13	blind$.ti,ab,kw,sh.	1335115
#14	(placebo$ or assign* or allocat* or volunteer*).ti,ab,kw,sh.	3245626
#15	(parallel$ or factorial$ or crossover* or cross over*).ti,ab,kw,sh.	1388712
#16	trial.ti.	1170871
#17	(multicent$ or multi-center$).af.	1281299
#18	('phase 3' or 'phase 2' or 'phase III' or 'phase II').af.	705708
#19	((single or double or triple) adj3 (blind* or mask* or dummy)).af.	1130584
#20	('double-blind' or 'double-blinded').af.	940981
#21	(open label or open-label).af.	269983
#22	("single arm" or "single arm" or "single group" or "single-group").ti,ab.	62502
#23	(meta analy* or meta-analy* or metanaly* or metaanaly*).ti,ab.	721079
#24	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.	721079
#25	(reference list* or bibliograph* or hand search* or manual search* or relevant journal*).ab.	147872
#26	(search strategy or search criteria or systematic search or study selection or data extraction).ab.	203470
#27	(search* adj4 literature).ab.	243032
#28	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.	911232

No.	Query	Results
#29	cochrane.jw.	58076
#30	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.	12717
#31	(addresses or bibliography or biography or case report or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lectures or letter or monograph or news or "newspaper article" or practice guideline or "review literature" or "review of reported cases" or review, academic or review, multicase or review, tutorial or twin study).pt.	4861925
#32	(animals/ not (humans/ and animals/)) or (animal/ not (human/ and animal/))	6448541
#33	case report/ or case reports/	5535308

A total of 1670 records were identified using the Ovid platform. Limits were applied to refine the results. These excluded studies not involving humans, studies not reported on in English, studies published before 2000, as well duplicates. This resulted in 1033 studies which went on to systematic screening of title and/or abstract.

H.1.2 Systematic selection of studies

All 1033 publications were independently reviewed against the inclusion/exclusion criteria detailed in Table 70 below, based on their abstract and title (Step 1). All papers included by the reviewer at the end of this first stage were retained for Step 2. Publications included after abstract review (from Step 1) were obtained for a full review of the text. All papers included after the full-text review were retained for data extraction. A record was kept of papers excluded at this stage along with a clear justification for their exclusion. Two independent reviewers screened all citations and full-text articles and any discrepancies in their decisions were resolved by a third independent reviewer. Data from included studies (from Step 2) were extracted into a pre-defined Excel-based template, ensuring that data were extracted uniformly and were comparable across studies. Two analysts independently extracted data and their results were checked and reconciled by a third independent analyst.

Table 70 Inclusion and exclusion criteria used for assessment of clinical studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	Patients diagnosed with advanced/metastatic or unresectable gastrointestinal stromal tumours (GIST)	Non-human Adjuvant/neoadjuvant setting Patients with GIST, receiving 1L-3L therapy	

	receiving fourth-line or more (≥4L) therapy		
Intervention	Ripretinib (DCC-2618)	Studies not including the intervention listed in the inclusion criteria Adjuvant or neoadjuvant therapy Radiotherapy Surgical procedures	
Comparators	Imatinib (Gleevec, Glivec, STI571), Regorafenib (Stivarga, Bay 73-4506), Sunitinib (Sutent, SU011248)) Other interventions studied for 4L+ GIST BSC	Studies not including at least one of the comparators listed in the inclusion criteria Adjuvant or neoadjuvant therapy Radiotherapy Surgical procedures	BSC only
Outcomes	Overall survival (OS) Progression-free survival (PFS), disease-free survival, event-free survival Response rate Duration of response, time to response Other efficacy endpoints Any safety endpoints QoL/PROs	Studies not including at least one of the outcomes listed in the inclusion criteria	OS, PFS, TTD, safety
Study design/publication type	Year limitation: 2000-current Randomised clinical trials (including extension studies) Single arm prospective interventional studies Sub-group analyses of previously published studies	Non-human/pre-clinical studies Reviews/ editorials/notes/comments/letters Non-interventional studies Retrospective studies Observational studies Uncontrolled studies Case reports/series	Randomised clinical trials with a comparator arm Preference for peer-review over abstract of same information

	Systematic reviews and meta-analyses (for cross-checking only) Pooled analyses (for cross checking)	
Language restrictions	English language	Non-English language studies

Abbreviations: BSC: Best supportive care, DCC-2618: Ripretinib, DFS: GIST: gastrointestinal stromal tumours, L: Line of therapy, OS: Overall survival, PFS: Progression-free survival, PROs: Patient-reported outcomes, TTD: Time to treatment discontinuation, QoL: Quality of life.

Of the 1033 records examined by title/abstract, 108 were selected for full-text review. Overall, following a full-text review and the addition of studies from congress, bibliographic search, and clinicaltrials.gov, a total of 32 records from 20 original studies were selected for data extraction in the clinical SLR. Details of the included and excluded studies are presented in the PRISMA flow diagram in Figure 38 for the original SLR and the local adaptation.

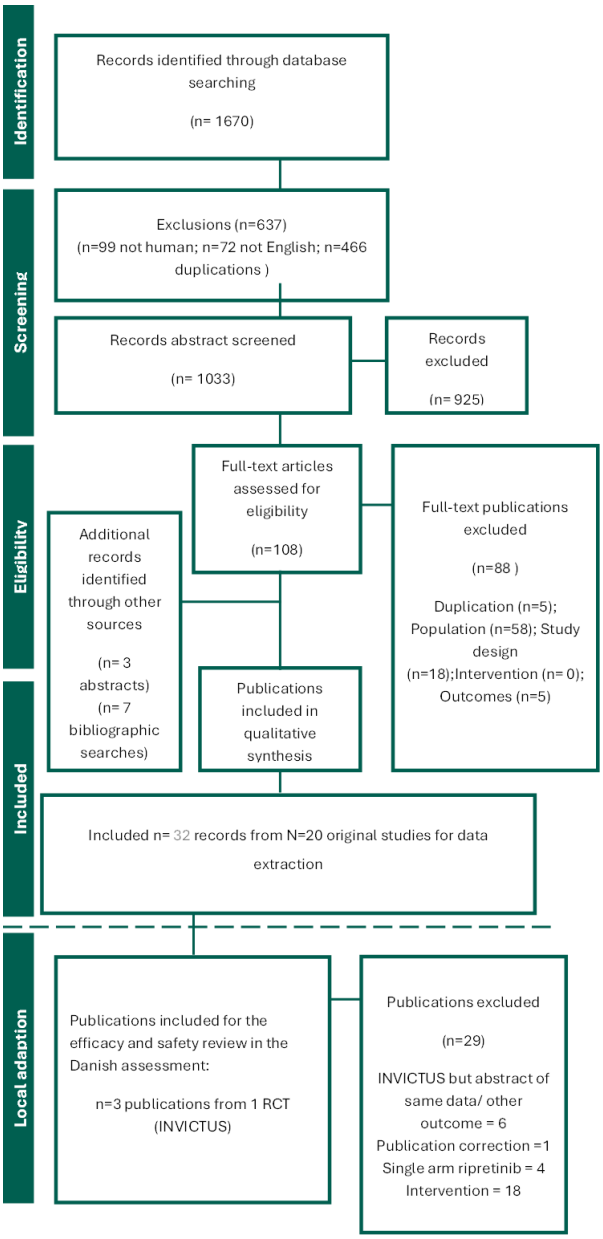


Figure 38 PRISMA flow diagram for Clinical Literature Search (08/04/2024)

Details of the 32 records are presented in Table 71, including reasons for exclusion or inclusion into the application. From these 20 original studies, the nine records relating to INVICTUS were identified as the most relevant for the current application, relating to the treatment comparison (ripretinib + BSC versus placebo + BSC) and patient population for the indication sought. From these INVICTUS records included in the SLR, two key records were applied in this application with regards to efficacy and safety: a peer-reviewed publication (Blay et al. 2020) as well as a conference abstract providing updated data to the peer-reviewed publication (von Mehren et al. 2021). A third was included from the SLR, but not directly applied in the application as for a later data cut of the pivotal publication but not the latest available data cut (Zalcberg et al. 2020). The remaining INVICTUS records (n=6) were excluded as were abstracts presenting same data as in the

peer-reviewed record, intervention dosing was not appropriate, or the outcome measures were not applied in this application. In addition, a correction to the Blay publication was considered excluded as related to the same publication and is not presented in the table below. This resulted in n=3 records from the SLR included and 29=excluded in the dossier.

Table 71 Results from the systematic literature review for the clinical analysis

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period	Reason for exclusion in the DMC dossier
Included records							
(Blay et al. 2020) (INVICTUS)	To compare the efficacy and safety of ripretinib, a switch-control tyrosine kinase inhibitor active against a broad spectrum of KIT and PDGFRA mutations, with placebo in patients with previously treated, advanced gastrointestinal stromal tumours.	RCT, phase 3 (double-blind phase)	Advanced GIST with progression on at least imatinib, sunitinib, and regorafenib or documented intolerance to any of these treatments despite dose modifications	Intervention: ripretinib + BSC (n=85) Comparator: placebo (n=44)	Progression-free survival Follow-up: randomisation until May 31, 2019	Overall survival, time to progression, time to best response, quality of life, safety. Follow-up: ongoing	Included
(von Mehren et al. 2021)	To present a long-term update of mature data from	RCT, phase 3 (double-blind phase)	Patients with advanced GIST previously treated with at least imatinib,	Intervention: ripretinib + BSC (n=85)	Progression-free survival	19 months after primary cut-off.	Included – abstract of new data cut

(INVICTUS - abstract)	the INVICTUS study.		sunitinib, and regorafenib	Comparator: placebo (n=43)	19 months after primary cut-off (January 15, 2021)		
(Zalcberg et al. 2020) (INVICTUS - abstract)	To report the updated safety results for ripretinib with an additional 9 months of follow-up.	RCT, phase 3 (double-blind phase)	Advanced GIST with progression on at least imatinib, sunitinib, and regorafenib or documented intolerance to any of these treatments despite dose modifications	Intervention: ripretinib + BSC (n=85) Comparator: placebo (n=43)	Progression-free survival Follow-up: until disease progression	Overall survival, safety. Follow-up: cut-off 9 months after primary results	Included – abstract of new data cut
Excluded records							
(Becker et al. 2022) (INVICTUS - abstract)	To provide further insight into outcomes at the patient level.	RCT, phase 3 (double-blind phase)	Patients with unresectable advanced 4L GIST	Intervention: ripretinib + BSC (n=85) Comparator: placebo (n=43)	Time to definitive deterioration, quality of life. Follow-up: NR	NR	abstracts presenting same data as in the peer-reviewed record / outcome
(George et al. 2020) (INVICTUS - abstract)	Impact of alopecia and Palmar-Plantar Erythrodysesthesia	RCT, phase 3 (double-blind phase)	Patients with advanced GIST previously treated with at least imatinib,	Intervention: ripretinib + BSC (n=85)	Adverse events and quality of life	NR	abstracts presenting same data as in the peer-

	Syndrome on quality of life		sunitinib, and regorafenib	Comparator: placebo (n=43)			reviewed record / outcome
(Zalcberg et al. 2021) (INVICTUS)	To report the efficacy and safety of ripretinib IPDE to 150 mg b.i.d. after PD among patients randomized to ripretinib 150 mg QD in the INVICTUS study.	RCT, phase 3 (double-blind phase)	Advanced GIST with progression on at least imatinib, sunitinib, and regorafenib or documented intolerance to any of these treatments despite dose modifications, in patients who received IPDE	Intervention: ripretinib (intrapatient dose escalation) (n=85) Comparator: ripretinib BID (n=44)	Progression-free survival Follow-up: until disease progression (9 March 2020)	Overall survival Follow-up: until patient death	Off-label dosing of intervention but indicates tolerability of ripretinib
(Serrano et al. 2020) (INVICTUS - abstract)	To evaluate the efficacy and safety of ripretinib for GIST patients following cross-over from placebo	RCT, phase 3 (open-label phase)	Patients with ≥4L advanced GIST previously treated with at least imatinib, sunitinib, and regorafenib	Intervention: placebo to ripretinib cross-over (n=85) Comparator: double-blind phase (n=43)	Progression-free survival Follow-up: until data cutoff 31/05/2019	Overall survival, safety. Follow-up: until data cutoff 31/05/2019	abstracts presenting same data as in the peer-reviewed record
(von Mehren et al. 2019) (INVICTUS abstract)	To assess the safety and efficacy of ripretinib as ≥ 4th-line therapy in patients with advanced	RCT, phase 3 (double-blind phase)	Advanced GIST with progression on at least imatinib, sunitinib, and regorafenib or documented intolerance to any of	Intervention: ripretinib + BSC (n=85) Comparator: placebo (n=43)	Progression-free survival Follow-up: until disease progression	Objective response rate, overall survival, safety. Follow-up: NR	abstracts presenting same data as in the peer-reviewed record

	gastrointestinal stromal tumors (GIST) who have received treatment with prior anticancer therapies		these treatments despite dose modifications				
(Bauer S. 2023) (INVICTUS)	To analyse quality of life and self-reported function with ripretinib in >=4th-line therapy for patients with gastrointestinal stromal tumours	RCT, phase 3 (double-blind phase)	Advanced GIST with progression on at least imatinib, sunitinib, and regorafenib or documented intolerance to any of these treatments despite dose modifications	Intervention: ripretinib + BSC (n=85) Comparator: placebo (n=44)	Progression-free survival Follow-up: until disease progression	Objective response rate, overall survival, quality of life. Follow-up: until data cutoff 31/05/2019	abstracts presenting same data as in the peer-reviewed record
(Li et al. 2022) (NCT04282980)	To analyse the efficacy and safety of ripretinib in Chinese patients with advanced gastrointestinal stromal tumours as a fourth- or later-line therapy with consistency to INVICTUS	Single arm, phase 2	Adult patients with advanced GIST who had progressed on prior three or more kinase inhibitors	Intervention: Ripretinib 150mg QD (n=39) No comparator	Progression-free survival Follow-up: until disease progression	Objective response rate, overall survival, time to best response, progression-free response rate based on investigator assessment, disease control	Study design/No comparator

						rate, safety markers. Follow-up: Ongoing	
(Li et al. 2023) (NCT04282980)	To update the analysis of efficacy and safety of ripretinib in Chinese patients with advanced gastrointestinal stromal tumors as a fourth- or later-line therapy with long-term results	Single arm, phase 2	Adult patients with advanced GIST who had progressed on prior three or more kinase inhibitors	Intervention: Ripretinib 150mg QD (n=38) No comparator.	Progression-free survival Follow-up: until disease progression	Objective response rate, overall survival, time to best response, progression-free response rate based on investigator assessment, disease control rate, safety markers. Follow-up: Ongoing	Study design/No comparator
(Chi et al. 2019) (NCT02571036)	To update the results of phase 1 study of ripretinib (DCC-2618), a broad-spectrum KIT and PDGFRA inhibitor, in patients with gastrointestinal stromal tumor	Single arm, phase 1	Patients with advanced GIST, receiving 150 mg QD Ripretinib (DCC-2618)	Intervention: Ripretinib (DCC-2618) (≥100 mg QD) (n=142) No comparator.	Progression-free survival Follow-up: until disease progression.	Objective response rate, best response, duration of response, safety. Follow-up: until data cutoff 10/08/2019	Study design/No comparator

	(GIST) by line of therapy						
(Janku et al. 2020) (NCT02571036)	To assess switch control inhibition of KIT and PDGFRA in patients with advanced gastrointestinal stromal tumor	Single arm, phase 1	Patients with with advanced GIST, intolerant to or experienced progression on ≥ 1 line of systemic therapy, and other advanced malignancies	Intervention: Ripretinib 150mg QD (n= 142) Escalation / expansion phases	Progression-free survival Follow-up: until disease progression	Maximum tolerated dose, safety, objective response rate, maximum observed concentration, time to maximum observed concentration, area under curve, half-life. Follow-up: until data cutoff 31/08/2019	Study design/No comparator
(Kurokawa et al. 2022) (CHAPTER-GIST-301)	To evaluate the efficacy and safety of pimitespib in advanced GIST refractory to standard TKIs.	RCT, phase 3 (double-blind phase)	Patients aged ≥ 20 years with histologically confirmed GIST who received prior treatment with imatinib, sunitinib, and regorafenib	Intervention: pimitespib (n=58) Comparator: placebo (n=28)	Progression-free survival Follow-up: until disease progression	Investigator assessed PFS, Overall survival, response rate, disease control rate, time to progression, open-label PFS.	Intervention

						Follow-up: data cutoff 23/06/2020	
(Qiu et al. 2023) (NCT03594422)	To assess antitumor activity of olverembatinib (HQP1351) in patients (pts) with tyrosine kinase inhibitor (TKI)–resistant succinate dehydrogenase (SDH)–deficient gastrointestinal stromal tumor (GIST).	Multi-arm	Patients aged ≥ 12 years with SDH-deficient GIST	Intervention: olverembatinib QOD (n=20)	Progression-free survival Follow-up: until disease progression	Safety, Follow-up: NR	Intervention/Study design/ Comparator
(Serrano et al. 2021) (SeliGIST/GEIS-41)	To evaluate the effect of selinexor in combination with imatinib in patients with advanced gastrointestinal stromal tumor	Single-arm, phase 1b/2	Patients with advanced GIST who were heavily pretreated	Intervention: Imatinib + Selinexor [Group 1 (60 mg), Group 1 (80 mg) and Group 1 (100 mg)] (n=NR) No comparator	Maximum tolerated dose Follow-up: 32 months	Progression-free survival, overall survival, objective response rate, incidence of TEAE, GIST genotype, drug plasma concentration, clinical benefit rate Follow-up: 32 months	Intervention / Study design / Comparator

(Chi et al. 2022) (NCT01991379)	To evaluate the safety and early efficacy signal of the combination of imatinib and binimetinib in patients with imatinib-resistant advanced gastrointestinal stromal tumors	Single-arm, phase 1b	Patients aged ≥18 years old with advanced GIST who had progressed on imatinib	Intervention: Imatinib + Binimetinib (n=23) Dose escalation / expansion	Safety, tolerability, maximum tolerated dose, RP2D. Follow-up: until data cutoff 01/05/2021.	Objective response rate, progression-free survival, overall survival, clinical benefit. Follow-up: until data cutoff 01/05/2021.	Intervention / Study design / Comparator
(Kang et al. 2021) (VOYAGER)	To evaluate the efficacy and safety of avapritinib versus regorafenib as third-line or later treatment in patients with unresectable or metastatic GIST	RCT, phase 3, open-label	Patients with locally advanced unresectable or metastatic GIST	Intervention: Avapritinib 300mg QD (n=240) Comparator: Regorafenib 160mg QD (n=236)	Progression-free survival Follow-up: until disease progression	Objective response rate, overall survival, safety, disease control rate, duration of response. Follow-up: until data cutoff 9/3/2020	Intervention / Comparator
(Serrano et al. 2019) (NCT02164240)	To study the rapid alternation of sunitinib and regorafenib for the treatment of tyrosine kinase	Single-arm, phase 1/2	Metastatic and/or unresectable GIST with prior failure to at least imatinib, sunitinib and regorafenib	Intervention: Sunitinib + Regorafenib (n=14) No comparator.	Safety, tolerability. Follow-up: until disease progression	Pharmacokinetics, efficacy. Follow-up: until disease progression	Intervention / Study design / Comparator

	inhibitor refractory gastrointestinal stromal tumors						
(Chi et al. 2015) (NCT01991379 - abstract)	To study binimetinib in combination with imatinib in patients with advanced gastrointestinal stromal tumour	Single arm, phase 1b	Imatinib-resistant advanced GIST	Intervention: Imatinib + Binimetinib (n=18) Dose escalation / expansion.	Safety, tolerability. Follow-up: until trial cutoff.	Progression-free survival. Follow-up: until disease progression	Intervention / Study design / Comparator
(Kelly et al. 2019) (NCT02257541)	To study infigratinib in combination with imatinib in patients with advanced gastrointestinal stromal tumour	Single-arm, phase 1b	Locally advanced or metastatic GIST that had progressed on imatinib	Intervention: Imatinib + infigratinib (n=16) No comparator.	Safety Follow-up: until disease progression	Clinical activity, pharmacokinetics. Follow-up: until disease progression	Intervention / Study design / Comparator
(Gelderblom et al. 2020) (NCT01468688)	To evaluate the combination of buparlisib, an oral phosphoinositide 3-kinase (PI3K) inhibitor, with imatinib in patients with advanced GIST, who have	Single-arm, phase 1b	Unresectable or metastatic GIST who had failed prior therapy with both imatinib and sunitinib	Intervention: Imatinib + Buparlisib (n=60) Dose escalation / expansions	Maximum tolerated dose Follow-up: NR	Clinical profile Follow-up: until disease progression	Intervention / Study design / Comparator / Outcome

	failed prior therapy with imatinib and sunitinib.						
(Bauer et al. 2014) (WTZ-GIST-09-01)	To determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLT) of panobinostat in combination with imatinib for treatment of patients with refractory GIST	Single-arm, phase 1b	Patients with metastatic GIST (aged 18 years and older) refractory to at least imatinib and sunitinib	Imatinib + Panobinostat	ORR Follow-up: NR	Safety Follow-up: NR	Intervention / Study design / Comparator
(George et al. 2023) (NCT05160168)	To report initial data from a first-in-human study in pts with advanced GIST (NCT05160168).	Single-arm, phase 1/2	Patients aged ≥ 18 years with unresectable/metastatic GIST previously treated with imatinib and at least 1 additional TKI	Intervention: THE-630 (n=19) Dose escalation / expansion.	Safety. Follow-up: NR	Pharmacokinetics, antitumour activity. Follow-up: NR	Intervention / Study design / Comparator / Ouctome
(Singh et al. 2022) (NCT02880020)	To analyse the efficacy of nivolumab (N) or nivolumab + ipilimumab (N + I)	RCT, phase 2, open-label, unblinded, parallel-group	Patients aged ≥18 years old with advanced/metastatic GIST	Intervention: nivolumab (n=19)	Objective response rate.	Progression-free survival, overall survival, response.	Intervention / Study design / Comparator

	in patients with refractory GIST.			Comparator: nivolumab + ipilimumab (n=16)	Follow-up: until disease progression.	Follow-up: until disease progression.	
(Mir et al. 2016) (PAZOGIST)	To assess the efficacy and safety of pazopanib in patients with previously treated advanced GIST.	RCT, phase 2	Adult patients (aged ≥18 years) with an unresectable, metastatic, or locally advanced histologically documented GIST resistant to imatinib and sunitinib, who had previously progressed on or discontinued due to toxic effects treatments	Intervention: pazopanib + BSC (n=40) Comparator: BSC (n=41)	Investigator-assessed progression-free survival. Follow-up: Until disease progression	Overall survival, response to treatment, objective response rate, drug plasma concentration, subgroup PFS. Follow-up: until disease progression / death	Intervention / Study design
(Ganjoo et al. 2014)	To evaluate the efficacy and toxicity of pazopanib in patients with advanced GIST following failure of at least imatinib and sunitinib.	Single-arm, phase 2	Patients with metastatic or unresectable GIST who progressed through or were intolerant of imatinib and sunitinib	Intervention: Pazopanib 800 mg orally QD (n=25) No comparator.	24-week non-progression rate Follow-up: until disease progression.	Progression-free survival, overall survival, toxicity. Follow-up: until disease progression/ death	Intervention / Study design

(Doi et al. 2019) (JapicCTI-163182)	To assess the efficacy and safety of pimitespib, in patients with metastatic or unresectable gastrointestinal stromal tumour refractory to imatinib, sunitinib and regorafenib	Single-arm, phase 2	Metastatic or unresectable GIST refractory to imatinib, sunitinib and regorafenib	Intervention: pimitespib 160mg QD (n=41) No comparator.	Progression-free survival Follow-up: until disease progression.	Objective response rate, disease control rate, overall survival, metabolic response rate, safety, pharmacokinetics, pharmacogenomics Follow-up: until disease progression/death.	Intervention / Study design
(Toulmonde et al. 2019) (CYCLIGIST)	To assess the activity and safety of palbociclib in patients with advanced gastrointestinal stromal tumors refractory to imatinib and sunitinib	Single arm, phase 2	Unresectable locally advanced or metastatic, refractory to previously treated with at least Imatinib and Sunitinib	Intervention: Palbociclib 125mg QD (n=71) No comparator.	4-month non-progression Follow-up: until disease progression.	Safety, progression-free survival, 1-eyar overall survival. Follow-up: until disease progression / 1 year	Study design / Intervention / Comparator
(Heinrich et al. 2019) (NAVIGATOR)	To assess the clinical activity of avapritinib in ≥ fourth-line (4L+)	Single arm, phase 1	Unresectable PDGFRA D842V or other mutant GIST who progressed on	Intervention: avapritinib (n=237) No comparator.	Safety, efficacy. Follow-up: until disease progression or	NR	Study design / Intervention / Comparator

	and PDGFRA Exon 18 gastrointestinal stromal tumours.		imatinib and ≥ 1 other TKIs		drug discontinuation		
(Chi et al. 2023) (NCT04936178)	To determine the safety and tolerability, the MTD, and the RP2D of NB003 in patients with advanced GIST.	Single arm, phase 1, dose-escalation	Confirmed GIST who progressed on or intolerant to imatinib and other standard of care treatments	Intervention: NB003 (n=23) Dose escalation.	Safety, tolerability. Follow-up: NR	Safety markers, PD, early efficacy signal by mRECIST. Follow-up: NR	Study design / Intervention / Comparator

Abbreviations: BID: Bis in die, twice daily, BSC: Best supportive care, GIST: Gastrointestinal stromal tumour, KIT: proto-oncogene c-KIT, n: number, NR: not reported, ORR: Objective response rate, PD: Progressive disease, PDGFRA: Platelet-derived growth factor reception A, PD: Progressed disease, PFS: Progression-free survival, QD: Quaque die, once daily, QoD: Every other day, RCT: Randomised controlled trial, RP2D: Recommended phase 2 dose, SDH: Succinate dehydrogenase, TEAE: Treatment-emergent adverse event, TKI: tyrosine kinase inhibitor.

H.1.3 Quality assessment

An assessment of quality was performed on abstracts, posters, or full-text articles of relevant RCTs using the NICE checklist. Reviewers independently ranked each included study and resolved any disagreement by reciprocal consulting.

The quality assessment was conducted of the relevant RCTs published in four studies including INVICTUS, VOYAGER, NCT02880020 and CHAPTER-GIST-301 (Table 72). The outcomes of this suggest that the literature obtained was overarchingly of high quality.

H.1.4 Unpublished data

No unpublished data was used in this review. In the [redacted]

Table 72 Quality assessment of the publications identified in the clinical SLR

Item	INVICTUS NCT03353753	Reference Blay et al. 2020 (Blay et al. 2020)	VOYAGER NCT03465722	Reference Kang et al. 2021 (Kang et al. 2021)	NCT02880020	Reference Singh et al. 2022 (Singh et al. 2022)	CHAPTER-GIST-301 JapicCTI184094	Reference Kurokawa et al. 2022 (Kurokawa et al. 2022)
Randomisation								
Was randomisation carried out appropriately?	YES	p.3	YES	p.2	YES	p.2	YES	p.2
Baseline Comparability								
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	YES	p.9	YES	p.5	YES	p.5	YES	p.5
Blinding								
Was the concealment of treatment allocation adequate?	YES	p.3	NO	p.2	NO	p.2	YES	p.2
Were the care providers, participants and outcome assessors blind to treatment allocation?	YES	p.3	NO	p.2	NO	p.2	YES	p.2

Follow-up								
Were there any unexpected imbalances in drop-outs between groups?	NO	p.4 Figure 1	NO	p.3 Figure 1	NOT CLEAR		NOT CLEAR	p.4 Figure 1
Selective Reporting								
Is there any evidence to suggest that the authors measured more outcomes than they reported?	NO	p.4	NO	p.3	NO	p.3	NO	p.2, p.3
Analysis								
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	YES	p.5	YES	p.3	YES	p.4	YES	p.3, p.4

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

As part of the wider SLR for clinical effect and safety, a search was conducted to identify information pertaining to the health-related quality of life (HRQoL) of advanced GIST patients. To collect utility data in each health state for GIST treatment, studies reporting utilities were identified using the following sources: HRQoL SLR (current appendix); Economic SLR (Appendix J) including both HTA review and Bibliographic search.

The process followed established practice and was comprised of the following core stages: definition of scope and agreement of search terms, implementation of searches and abstract review to inform included papers, and extraction and quality assessment of data.

The scope of the SLR was defined in terms of criteria using the PICOS statement as described in Table 73 below. The target patient population included in SLR was patients diagnosed with advanced/metastatic GIST undergoing any line of therapy. The intervention of interest was ripretinib, with comparators chosen based on currently approved treatments for 4L+ GIST or advanced GIST. Outcomes were used to ensure that the studies reported the relevant QoL data. For the HRQoL SLR, study designs that were likely to report HRQoL and utility data for metastatic GIST were included in this review. Other SLRs and meta-analyses were used to ensure that all relevant QoL data were captured.

Table 73 PICOS statement for the HRQoL SLR in metastatic GIST

QoL PICOS	
Patient population	• Patients diagnosed with metastatic or unresectable GIST (i.e. advanced) • Any line of therapy
Intervention and Comparators	• No restriction
Outcome measures	• QoL • PROs • Utilities
Study design	• Reports of randomised clinical trials assessing HRQoL • Observational studies measuring PROs • Retrospective chart audits and database analyses reporting PROs

- Patient surveys reporting PROs
- Reports of mapping exercises for any outcome measure to utility
- Reports of utility elicitation exercises
- Reports of utility validation exercises
- Reports of economic evaluations using utility measures elicited during the studies

Abbreviations: GIST: Gastrointestinal stromal tumours, HRQoL: Health-related quality of life, PRO: Patient-reported outcomes, QoL: Quality of life.

The key biomedical literature databases (Medical Literature Analysis and Retrieval System Online [MEDLINE®], Excerpta Medica Database [Embase®]) and Cochrane collaboration were consulted as described in Table 74. This is in accordance with the list of databases suggested by several HTA organisations, such as the CADTH (Canada) and NICE (England and Wales). MEDLINE® Epub Ahead of Print, In-Process as well as other non-indexed citations were searched to ensure that non-indexed citations would also be retrieved.

Table 74 Bibliographic databases included in the HRQoL literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Ovid	2000-present	08.04.2024
Medline	Ovid	2000-present	08.04.2024
Cochrane	Ovid	2000-present	08.04.2024

Other sources were used to enrich the search. The bibliographies of systematic reviews and meta-analyses identified through database searches were used to identify key studies. Furthermore, bibliographies from selected studies were reviewed to identify studies relevant to the SLR. This process ensured that papers and articles not identified in the initial search were included in the review. In addition, the websites of the regulatory and HTA authorities in the countries of interest were consulted, which included the UK (England and Scotland), Australia, and Canada: NICE - National Institute for Health and Care Excellence, SMC - Scottish Medicines Consortium, PBAC - Pharmaceutical Benefits Advisory Committee, CADTH - Canadian Agency for Drugs and Technologies in Health. The selected countries represent larger reimbursement markets and provide the most robust resources for the identification of relevant documents. These other sources are detailed in Table 75.

Table 75 Other sources included in the HRQoL literature search

Source name	Location/source	Search strategy	Date of search

Bibliographies	Systematic reviews and meta-analyses found through database searches	Review of all systematic review and meta-analysis bibliographies.	30.04.2024
NICE	www.nice.org.uk	Searches for relevant literature using key words in website-based search function.	30.04.2024
SMC	www.scottishmedicines.org.uk	Searches for relevant literature using key words in website-based search function.	30.04.2024
PBAC	www.pbac.pbs.gov.au	Searches for relevant literature using key words in website-based search function.	30.04.2024
CADTH	www.cadth.ca	Searches for relevant literature using key words in website-based search function.	30.04.2024

Abbreviations: NICE: National Institute for Health and Care Excellence, SMC: Scottish Medicines Council, PBAC: Pharmaceutical Benefits Advisory Committee, CADTH: Canadian Agency for Drugs and Technology in Health.

Conference abstracts were searched from 2017 to 2024 to retrieve the latest studies, using the search terms: “GIST”, “Gastrointestinal stromal tumor”, and “Gastrointestinal stromal tumour”. The conference proceedings of the following organisations were searched manually for abstracts: ASCO (2018-2023), ASCO GI (2018-2024), and ESMO (2017-2023). This is detailed in Table 76 below.

Table 76 Conference material included in the HRQoL literature search

Conference	Source of abstracts	Search strategy	Words/Terms searched	Date of search
American Society of Clinical Oncology (ASCO)	Conference proceedings	Manual search (2018-2023)	"GIST”, “Gastrointestinal stromal tumour”, and “Gastrointestinal stromal tumour”	April 2024
American Society of Clinical Oncology Gastrointestinal Symposium (ASCO GI)	Conference proceedings	Manual search (2018-2024)	“GIST”, “Gastrointestinal stromal tumour”, and “Gastrointestinal stromal tumour”	April 2024

European Society for Medical Oncology (ESMO)	Conference proceedings	Manual search (2017-2023)	"GIST", "Gastrointestinal stromal tumour", and "Gastrointestinal stromal tumour"	April 2024

I.1.1 Search strategies

The Ovid platform was used to conduct searches in the literature databases mentioned. Data were obtained by combining extensive lists of search terms for the indication, interventions, and study designs. Search strings per database were developed based on the PICOS framework described in Table 77, Table 78, and across all databases in Table 79.

Table 77 Search strategy for Medline for the HRQoL SLR

No.	Query	Results
#1	Gastrointestinal Stromal Tumors/	17677
#2	Neoplasm Metastasis/	318305

Table 78 Search strategy for Embase for the HRQoL SLR

No.	Query	Results
#1	gastrointestinal stromal tumor/	30038
#2	metastasis/ or advanced cancer/	611891

Table 79 Search strategy for all databases for the HRQoL SLR

No.	Query	Results
#1	(gastrointestinal stromal tumor$ or gastro-intestinal stromal tumor$ or gastro intestinal stromal tumor$ or gastrointestinal stromal tumour$ or gastro-intestinal stromal tumour$ or gastro intestinal stromal tumour$).ti,ab.	28482
#2	(gastrointestinal stromal neoplasm$ or gastro-intestinal stromal neoplasm$ or gastro intestinal stromal neoplasm$).ti,ab.	11
#3	(gastrointestinal stromal sarcoma$ or gastro-intestinal stromal sarcoma$ or gastro intestinal stromal sarcoma$).ti,ab.	39
#4	GIST.ti,ab.	23414
#5	(metasta$ or advanced or unresectable or un-resectable or non-resectable or nonresectable).ti,ab.	2973221
#6	"quality of life"/	987590

#7	(QOL$ or HQL$ or HQOL$ or H QOL$ or HRQL$ or HRQOL$ or HR QOL$).ti,ab.	263214
#8	(quality adj4 life).ti,ab.	1204594
#9	(quality adj2 well?being).ti,ab.	1660
#10	Quality-Adjusted Life Years/ or quality adjusted life year/	58926
#11	(quality adjusted life$ or quality-adjusted life$ or disability adjusted life$ or disability-adjusted life$).ti,ab.	65575
#12	(QALY or qal$ or qwb$ or qald$ or qale$ or qtime$ or daly$).ti,ab	63651
#13	Patient Reported Outcome Measures/ or patient-reported outcome/	76713
#14	(patient adj2 reported adj2 outcome$).ti,ab.	115260
#15	PRO.ti,ab.	682844
#16	(euroqol$ or euro qol$ or euro-qol$ or euroqual$ or euro qual$ or euro-qual$ or eq5d$ or eq 5d$ or eq-5d$ or eqoL-5d$ or eqoL5D$ or eqoL 5d$).mp,af,tw.	67626
#17	(utilit$ or disutilit$).mp,af,tw.	780492
#18	(standard gamble$ or time-trade-off or time trade-off or time trade off or time tradeoff).ti,ab.	5824
#19	(willingness adj4 pay).ti,ab.	32464
#20	(SG or TTO or WTP).ti,ab.	52213
#21	((valu$ or measur$) adj4 (health or outcome$ or effect$ or change$ or state$)).ti,ab	1804872
#22	(VAS or visual analogue scale$ or visual-analogue scale$).mp,af,tw.	305200
#23	(sf-36$ or sf36$ or sf 36$ or sf-12$ or sf12$ or sf 12$ or sf-6$ or sf6$ or sf 6$ or short form$ or shortform$ or RAND$).mp,af,tw.	6109637
#24	("European Organization for Research and Treatment of Cancer" or EORTC or QLQ-C30 or QLQ C30 or QLQC30).mp,af,tw.	62008
#25	(Functional Assessment of Cancer Therapy or FACT-G or FACTG or FACT G or FACT-General or FACT General or FACT-F or FACTF or FACT F or FACT-Fatigue or FACT Fatigue).mp,af,tw.	13245
#26	("Hospital Anxiety and Depression Scale" or HADS or EORTC-QLQ STO22 or EORTC QLQ-STO22 or EORTC QLQ STO22 or EORTC-QLQ-STO22 or FACT-Ga or FACT Ga or Gastrointestinal Quality of Life Index or GIQLI).mp,af,tw.	56805

A total of 1894 records were identified using the Ovid platform. Limits were applied to refine the results. These excluded studies not involving humans, studies not reported on in English, studies published before 2000, as well duplicates. This resulted in 1233 studies which went on to systematic screening of title and/or abstract.

I.1.2 Systematic selection of literature

All 1233 publications were independently reviewed against the inclusion/exclusion criteria based on their abstract and title. All papers included by the reviewer at the end of this stage were retained for Step 2. Publications included after abstract review (from Step 1) were obtained for a full review of the text. All papers included after the full-text review were retained for data extraction. A record was kept of papers excluded at this stage along with a clear justification for their exclusion. Two independent reviewers screened all citations and full-text articles and any discrepancies in their decisions were resolved by a third independent reviewer. Data from included studies (from Step 2) were extracted into a pre-defined Excel-based template, ensuring that data were extracted uniformly and were comparable across studies. Two analysts independently extracted data and their results were checked and reconciled by a third independent analyst. The specific inclusion and exclusion criteria are summarised in Table 80 below.

Table 80 Inclusion and Exclusion Criteria for HRQoL Systematic Literature Review

Element	Inclusion	Exclusion	Changes, local adaptation
Patient population	Patients diagnosed with advanced/metastatic or unresectable GIST At any line of therapy	Non-human Adjuvant/neoadjuvant setting	Late line advanced GIST Multicounty or if single country - European
Intervention and Comparators	No restriction	Studies not including at least one of the interventions listed in the inclusion criteria	Ripretinib, regorafenib or no longer on treatment if having had ≥3L treatment
Outcome measures	QoL PROs Utilities	Studies not including at least one of the outcomes listed in the inclusion criteria	EQ5D instrument (utility score or VAS)
Study design	Reports of randomized clinical trials assessing HRQoL Observational studies measuring PROs	Reviews Editorials Notes/comments/letters	RCT or observational studies assessing PROs/HRQoL

	Retrospective chart audits and database analyses reporting PROs Patient surveys reporting PROs Reports of mapping exercises for any outcome measure to utility Reports of utility elicitation exercises Reports of utility validation exercises Reports of economic evaluations using utility measures elicited during the studies Systematic reviews and meta-analyses (for cross-checking only)	
Restrictions	English language Year limitation: 2000-current	Non-English language studies

Abbreviations: EQ-5D: EuroQoL Five-Dimension questionnaire, GIST: Gastrointestinal stromal tumour, HRQoL: Health-related quality of life, L: Line of therapy, PRO: Patient-reported outcome, VAS: Visual analogue scale.

Of the 1223 records selected for abstract review, 60 were selected for full-text review, after screening by title/abstract. Overall, following a full-text review and the addition of studies from the bibliographic search and congress review, a total of 34 records from 24 original studies were selected for data extraction in the HRQoL SLR. Details of the included and excluded studies across the three SLR searches are presented in the PRISMA flow diagram in Figure 39 for the original SLR and the local adaptation.

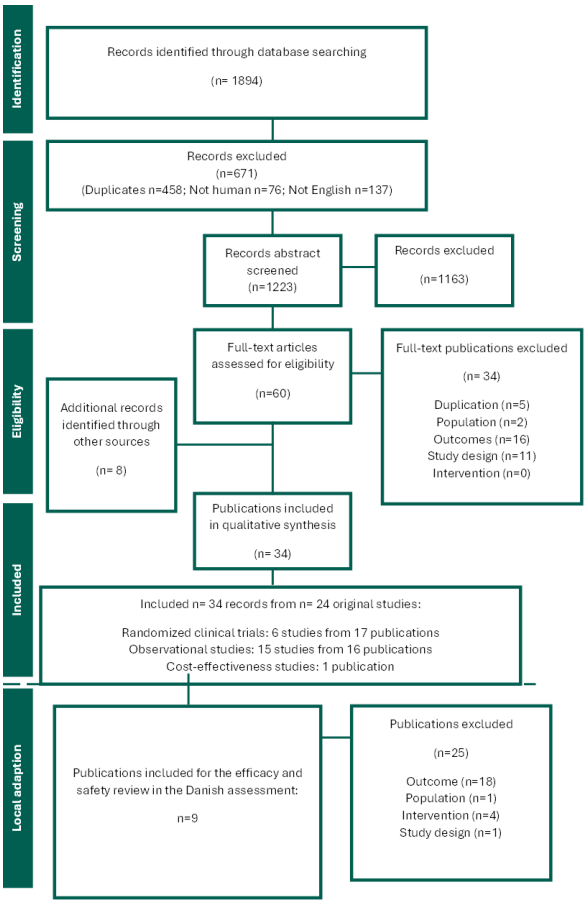


Figure 39 PRISMA flow diagram for HRQoL Literature Search

A summary of the HRQoL SLR results is presented in Table 81 below, including the reasons for exclusion (if relevant) from the local adaptation of this existing SLR. In total, nine publication records were deemed relevant and included in the local adaptation of the SLR. These came from two RCTs: INVICTUS (n=7) and GRID (n=2). Owing to the duplication of data across these publications from the same source RCTS, two key publications have been directly utilised in this application namely Poole et al. for GRID data and Schöffski et al for INVICTUS data (Poole et al. 2015).

Table 81 Results from the Systematic Literature Review for HRQoL

Reference	Title	Interventions	Study design	Study population	Scales used	Findings	Reason for exclusion in DMC dossier
Included records							
(Schöffski et al. 2022) (INVICTUS)	PROs in individuals with advanced GIST treated with ripretinib in the fourth-line setting: analysis from the phase 3 INVICTUS trial.	Ripretinib vs placebo (PBO)	RCT, phase 3	Patients with advanced GIST with progression on at least imatinib, sunitinib, and regorafenib or documented intolerance to any of these treatments despite dose modifications	EORTC QLQ-C30, EQ-5D-5L	Patients receiving ripretinib maintained their daily self-reported health on the EQ-5D VAS, while PBO treatment was associated with a decline (nominal p=0.004 for the difference between arms). Patients receiving ripretinib reported stable physical and role functioning relative to baseline, and the same measures deteriorated in patients receiving PBO (nominal p=0.004 and nominal p=0.001, respectively). Patients also maintained stable perceptions of their overall health and QoL compared with the PBO arm (both nominal P=0.001). All differences between treatment arms exceeded the MCID. Longitudinal changes in PRO scores from baseline in the ripretinib arm show that patients receiving ripretinib reported stable role and physical function, health status, and health QoL out to cycle 10, day 1 (approximately 8 months), which	Include

						exceeds the previously reported median progression-free survival.	
(Jones et al. 2022) (INVICTUS)	Health State Utility Values and Quality of Life in Patients Receiving Ripretinib in the Phase 3 Invictus Trial and a Real-World Evidence Study in China.	Ripretinib vs Placebo (PBO)	RCT, phase 3	Patients with advanced GIST with progression on at least imatinib, sunitinib, and regorafenib or documented intolerance to any of these treatments despite dose modifications	EQ-5D-5L	Data were mapped using UK value sets to EQ-5D 3-Level utilities. EQ-5D completion was >99%. HSUV for R vs. PBO were 0.75 vs. 0.73 for progression-free patients and 0.75 vs. 0.71 for progressive disease patients. In the RWE study, EQ-5D completion was 65%. HSUV were 0.81 for progression-free patients and 0.67 for progressive disease patients.	Include
(Reichardt 2021) (INVICTUS)	Safety profile of ripretinib, including impact of alopecia, and palmar-plantar erythrodysesthesia on PROs, in >= fourth-line advanced GIST: Analyses from INVICTUS.	Ripretinib vs Placebo (PBO)	RCT, phase 3	4L Patients with advanced GIST previously treated with at least imatinib, sunitinib, and regorafenib.	EQ-5D-5L, EORTC QLQ-C30	The only association reaching a p-value of <0.05 was between alopecia and increased overall QoL. None of the associations between palmar-plantar erythrodysesthesia and PRO scores reach $p < 0.05$. All PRO p-values are nominal, and no statistical significance is being claimed. When stratified by alopecia and palmar-plantar erythrodysesthesia , patient-reported assessments of function, overall health, and overall QoL were maintained over time. These results suggest that alopecia and palmar-plantar erythrodysesthesia are	Include

						manageable and do not have a negative effect on function, overall health, and QoL.	
(Blay et al. 2020) (INVICTUS)	Ripretinib in patients with advanced GISTs (INVICTUS): a double-blind, randomised, PBO-controlled, phase 3 trial.	Ripretinib vs Placebo (PBO)	RCT, phase 3	Advanced GIST with progression on at least imatinib, sunitinib, and regorafenib or documented intolerance to any of these treatments despite dose modifications	EORTC-QLQ-C30, EQ-VAS	The role and physical functioning (as assessed by EORTC-QLQ-C30) from baseline to cycle 2 day 1 remained stable in the ripretinib group with adjusted mean change in score of 3.5 (95% CI –3.4 to 10.5) for role functioning and 1.6 (–2.5 to 5.7) for physical functioning, compared with a decrease with PBO of 17.1 for role functioning (95% CI –27.0 to –7.1) and a decrease of 8.9 for physical functioning (–14.8 to –3.0). Overall health (as assessed by EQ-VAS) from baseline to cycle 2 on day 1 also remained stable in the ripretinib group with adjusted mean change in scores of 3.7 (95% CI –1.1 to –8.6) compared with a decrease in the group that received PBO of 8.9 (–15.9 to –1.9). Using either QoL instrument, the results showed a clinically relevant difference between ripretinib and placebo.	Include
(George et al. 2020) (INVICTUS)	Safety profile of ripretinib, including impact of alopecia, and Palmar-Plantar Erythrodysesthesia Syndrome on patient-reported	Ripretinib vs Placebo (PBO)	RCT, phase 3	Advanced GIST with progression on at least imatinib, sunitinib, and regorafenib or documented intolerance to any of	EORTC-QLQ-C30, EQ-VAS	The repeated measures models showed a slight trend towards improvement in PRO score over time for patients with alopecia; the only association reaching a p-value of < 0.05 was between alopecia and increased overall QoL.	Include

	outcomes (PROs), in ≥ fourth-line advanced gastrointestinal stromal tumors (GIST): Analyses from INVICTUS.			these treatments despite dose modifications			
(Heinrich et al. 2020) (INVICTUS)	Quality of life (QoL) and self-reported function with ripretinib in ≥4th-line therapy for patients with gastrointestinal stromal tumors (GIST): Analyses from INVICTUS.	Ripretinib vs Placebo (PBO)	RCT, phase 3	Advanced GIST with progression on at least imatinib, sunitinib, and regorafenib or documented intolerance to any of these treatments despite dose modifications	EORTC-QLQ-C30, EQ-VAS	The EQ-5D VAS scores improved an average 3.7 points from baseline to cycle 2 day 1 with ripretinib vs an average decline of 8.9 with PBO (p = 0.004; improvement or no change, 67% vs 41% of patients, respectively). Similarly, the average EORTC QLQ-C30 physical functioning score improved 1.6 points with ripretinib and decreased 8.9 with PBO (P = 0.004; improvement or no change, 68% vs 44%). EORTC-QLQ-C30 role functioning scores also improved an average of 3.5 points with ripretinib vs a decrease of 17.1 with PBO (p= 0.001; improvement or no change, 77% vs 50%). For the overall health and overall QoL questions, scores increased with ripretinib an average of 0.20 and 0.28, respectively, and decreased 0.78 and 0.76 with PBO (both p=0.001; improvement or no change, 74% vs 47% and 79% vs 59%, respectively).	Include

(Bauer S. 2023) (INVICTUS)	Quality of life and self-reported function with ripretinib in >=4th-line therapy for patients with gastrointestinal stromal tumours: Analyses from INVICTUS.	Ripretinib vs Placebo (PBO)	RCT, phase 3	Advanced GIST with progression on at least imatinib, sunitinib, and regorafenib or documented intolerance to any of these treatments despite dose modifications	EQ-5D VAS, EORTC-QLQ-C30	Mean EQ5D VAS scores improved 3.7 points from baseline to C2D1 with ripretinib and declined 8.9 points with PBO (p = 0.004). Mean EORTC-QLQ-C30overall health and QoL scores increased with ripretinib by 0.20 and 0.28 and decreased 0.78 and 0.76 with placebo, respectively (both p = 0.001). Compared with placebo and best supportive care, ripretinib provided meaningful QoL benefit in patients with 4L advanced GIST; PRO measures of role functioning, physical functioning, VAS scores, overall health, and overall QoL remained stable.	Include
(Poole et al. 2015) (GRID)	Health utility of patients with advanced GIST after failure of imatinib and sunitinib: findings from GRID, a randomized, double-blind, PBO-controlled phase III study of regorafenib vs placebo	Regorafenib 160 mg daily + BSC vs placebo (PBO) + BSC	RCT, phase 3	Advanced GIST	EQ-5D-3L	There were no significant between-group differences in baseline EQ-5D score for either treatment arm, line of therapy, or those among whom disease progression occurred. There was a statistically significant mean difference of -0.120 (p = 0.001) between baseline- and first post-progression utility. An intermediate main-effects model that included progression state, treatment cycle number, and treatment type reveals that while adjusting for progression state, neither cycle number (p = 0.341) nor treatment type (off-treatment vs. regorafenib, p = 0.749; PBO	Include

						vs. regorafenib, p = 0.233) significantly influences observed utility. Removal of nonsignificant fixed effects leaves a model with one random effect [subject (random intercept and slope)] and one fixed effect, disease progression state. In this model the mean utility difference between the progression-free state and post-progression state, at -0.041, is smaller than that observed between the point estimates at baseline and first post-progression observation, but of threshold statistical significance (p = 0.051). The mean utility for subjects following second disease progression was significantly lower than progression-free state at -0.231 (p<0.001).	
(Zolic et al. 2015) (GRID)	Estimating quality of life for patients with gist based on patient reported EQ5D scores and Swedish utility weights in order to inform a cost-effectiveness model for regorafenib.	Regorafenib vs Placebo (PBO)	RCT, phase 3	Metastatic and/or unresectable GIST	EQ-5D	Based on the paired samples analysis, the progression-free state is associated with a utility of 0.872, while the post progression state is associated with a utility of 0.806. The difference of 0.066 is significant at p = 0.0117. A utility of 0.850 for the progression-free state and 0.814 for the progressed disease state was estimated using the simplest repeated measures model, not including variables for treatment effect. Extension of the time to progression in a population treated for GIST	Include

						will be associated with a QALY gain in range of 0.035 to 0.066 per year.	
Excluded records							
(Bauer et al. 2022) (INTRIGUE)	Ripretinib Vs Sunitinib in Patients With Advanced GIST After Treatment With Imatinib (INTRIGUE): A Randomized, Open-Label, Phase III Trial.	Ripretinib vs Sunitinib	RCT, phase 3	Patients with advanced GIST after treatment with imatinib	DLQI, EORTC QLQ-C30	Patients used the DLQI to assess impact of skin issues on QoL because of high incidence of dermatologic AEs reported with sunitinib. Impact on QoL was less frequently reported with ripretinib versus sunitinib across treatment cycles (Cycle 7 Day 29: 14.3% vs 26.0%). Patients receiving sunitinib also experienced greater deterioration in EORTC QLQ-C30 role functioning across all treatment cycles (mean change from baseline at Cycle 7 Day 29: 28.7 vs 222.7 for ripretinib vs sunitinib). In both measures, patients receiving sunitinib reported less impact/deterioration on day 1 of each cycle immediately following the 2-week off period compared with day 29, whereas ripretinib scores did not demonstrate cyclical variation.	Outcome scale / Patient group
(Gelderblom et al. 2022) (INTRIGUE)	Patient reported outcomes and tolerability in patients receiving ripretinib vs	Ripretinib vs Sunitinib	RCT, phase 3	Patients with advanced GIST after treatment with imatinib	DLQI, EORTC QLQ-C30	Significant differences in self-reported functioning and symptoms were observed by Cycle 1 Day 29. For PROs relating to commonly reported serious treatment-related AEs, except constipation, patients in	Outcome scale / Patient group

	sunitinib after imatinib treatment in INTRIGUE: A phase 3 open-label study.					the ripretinib arm reported better outcomes than in the sunitinib arm. Patients in the ripretinib arm reported significantly ($p<0.05$) less decline compared to baseline in patient-reported role function as well as less increase, or improvement, in symptoms of fatigue, appetite loss, diarrhoea, nausea/vomiting, and pain vs patients in the sunitinib arm. Moderate or severe effect of skin toxicity on patient life, as measured by DLQI in the ripretinib arm (n = 165) and in the sunitinib arm (n = 175), was observed in 6.6% of patients in the ripretinib arm vs 14.8% of patients in the sunitinib arm (p = 0.015).	
(Gelderblom et al. 2023) (INTRIGUE)	Patient-reported outcomes and tolerability in patients receiving ripretinib versus sunitinib after treatment with imatinib in INTRIGUE, a phase 3, open-label study.	Ripretinib vs Sunitinib	RCT, phase 3	Patients with advanced GIST after treatment with imatinib	EORTC QLQ-C30	Patients receiving ripretinib generally reported better outcomes than patients receiving sunitinib across functional scales. Average deterioration from baseline role functioning and physical functioning rarely exceeded the MCID for patients receiving ripretinib across the first 9 cycles (54 weeks) of treatment for both Day 1 and Day 29 assessments. On Day 29 assessments, patients receiving sunitinib generally experienced greater deterioration from baseline that exceeded the MCID in EORTC QLQ-C30 role functioning and physical functioning compared with ripretinib	Outcome scale / Patient group

						patients across cycles. Patients receiving ripretinib generally reported better outcomes than patients receiving sunitinib across all QLQ-C30 symptom scales except constipation. Patients receiving ripretinib and sunitinib generally experienced similar change from baseline in QLQ-C30 symptom scales on Day 1 assessments across cycles, but on Day 29 assessments, patients receiving sunitinib generally experienced greater increase in symptoms from baseline in QLQ-C30 fatigue, pain, appetite loss, nausea and vomiting, and diarrhoea compared with ripretinib patients.	
(Becker et al. 2022) (INVICTUS)	POSB342 Time Until Definitive Deterioration in PROs in a Phase 3 Trial for Ripretinib in 4L Patients with GIST	Ripretinib vs Placebo (PBO)	RCT, phase 3	4L Patients with advanced GIST.	EQ-5D-5L VAS, EORTC QLQ C30	Patients on ripretinib had longer time in each of functioning, health and QoL, and VAS than placebo. Patients on PBO reported time to definitive deterioration within a median 8 weeks, while the median time to definitive deterioration in overall health was not reached for patients on ripretinib. For the physical and role functioning, and the VAS, the time to definitive deterioration was 41.6 weeks. Ripretinib patients reported being able to maintain QoL, health, and physical and role functioning, while these measures declined sharply in the PBO arm. In this heavily pretreated 4L GIST population, QoL is an	Outcome

						important aspect of treatment success. For patients on ripretinib, median time to definitive deterioration was 5 times as long as those on PBO. Median time until definitive deterioration was not shorter than median PFS. The average difference between the two arms was both clinically and statistically significant.	
(Zhang et al. 2023) (NCT05697107)	Large-Scale, Multicenter, Prospective Registry Study of Ripretinib in Advanced GIST: A Real-World Study from China.	Ripretinib	Prospective observational study	Histologically confirmed recurrent/metastatic GIST	EQ-5D	The mean health utility values of progression-free and progressive disease health states were 0.8 (95% CI 0.8–0.8) and 0.7 (95% CI 0.6–0.7), respectively, suggesting that the reduction in QoL of patients due to AEs following ripretinib treatment was low. The average score of VAS reported by patients at baseline and at every 2 months follow-up showed that the patient's health status remained stable during the treatment, suggesting that ripretinib was well tolerated.	Population
(Ahmed et al. 2023) (NCT03739827)	Longitudinal Natural History Study of Children and Adults with Rare Solid Tumors: Initial Results for	NR	Longitudinal natural history study	Children and adults with solid tumours (GIST reported separately)	PROMIS	PROMIS Measure, mean (SD): Anxiety (N=20): 54.9 (7.1); 4 (20%) with clinically significant response Depression (N=20): 47.8 (8.0); 1 (5%) with clinically significant response	Population/ Outcome

	First 200 Participants.					Pain interference (N=20): 51.7 (8.8); 3 (15%) with clinically significant response	
(van de Wal et al. 2023a)	Psychological and social challenges of patients with locally advanced and metastatic gastrointestinal stromal tumours (GIST) on long-term treatment with tyrosine kinase inhibitors: a qualitative study with patients and medical oncologists	Imatinib	Qualitative and exploratory study, semistructured interviews	Locally advanced or metastatic GIST treated with a TKI for ≥5 years	NR	Patients expressed fears about the disease becoming resistant to TKI treatment, disease progression, death and disease activity when experiencing a physical sensation. The majority of patients emphasised feeling anxious around regular tests, scans and follow-up visits. Some patients acknowledged constantly being reminded of their illness due to the daily side effects of treatment, comments from others, having to take medication (daily) or regular scans and follow-up visits. Patients expressed multiple doubts while on treatment, most frequently about stopping their TKI. They underlined the fear of progression when stopping, and the fear of not responding to treatment when needing treatment again. However, none of the patients actually had stopped taking TKIs because they felt more secure while being on treatment. Patients underlined that they had to change or give up their hobbies or had to negatively adjust their social activities, including shorten the duration or slowing down during activities. 3 patients expressed having to plan activities or that planned activities are always subjected to	Outcome

						change due to the experienced, sometimes unexpected, side effects. 2 patients had trouble functioning in big groups, and described not feeling comfortable. Patients expressed not being able to find a partner or losing friends. Patients also emphasised feeling a burden to others for various reasons, among which, still being alive while diagnosed with cancer or having to cancel activities with friends due to side effects such as fatigue. Financial difficulties were also frequently mentioned.	
(Kurokawa et al. 2022) (CHAPTER-GIST-301)	Pimitespib in patients with advanced GIST (CHAPTER-GIST-301): a randomized, double-blind, PBO-controlled phase III trial.	Pimitespib vs placebo (PBO)	RCT, phase 3	Patients with advanced GIST refractory to imatinib, sunitinib, and regorafenib	EORTC QLQ-C30	With respect to HRQoL, no significant difference was observed in the time to deterioration of 10 points in global health status between pimitespib and PBO.	Intervention
(FAUSKE et al. 2022)	Hope as a Lifeline: Imatinib Discontinuation in Patients With Oligometastatic GISTs	Imatinib discontinuation	Prospective observational study	Patients who had a confirmed diagnosis of metastatic GIST and had received TKI therapy involving imatinib for longer than five years for oligometastatic	NR	Prior to discontinuing imatinib, 6 of the 9 participants described how the side-effects of the treatment had a detrimental effect on their lives. Some expressed how tiredness, including the resultant impaired memory, and physical challenges were among the complaints that had the most significant detrimental impacts on their	

				GISTs (≤3 metastases) that were initially documented to be responding to treatment.		lives, with some having to adjust their daily activities to make it through the day. Once the side-effects had subsided or disappeared following discontinuation of imatinib, they reported having a surplus of energy, enjoying improved mental health and experiencing less challenges in daily life. The phenomenon of 'getting one's life back' after discontinuing imatinib is something that all of the participants experienced to some degree or another. Participants also reported varying degrees of uncertainty regarding the possibility of recurrence after discontinuing imatinib and the implications that recurrence would have for their lives.
(van de Wal et al. 2023b)	A patient's perspective on the side effects of tyrosine kinase inhibitors in the treatment of advanced and metastatic GISTs	TKIs	Prospective observational study	Patients with 4L advanced GIST	NR	Symptoms relating to gastrointestingal problems were reported by all participants; Diarrhoea was not only the most commonly reported symptom, but was also identified by 5 participants as the most troublesome symptom affecting everyday activities, including social functioning, and requiring careful management, resulting in the introduction of antidiarrheal medications or dose reductions. 10 patients referred to fatigue as the most troublesome of all side effects, leading to adjustments in their daily lives (e.g., needing more rest, going to bed

						early), dose reductions or the need to take sleeping tablets. Healthcare professionals seem to underestimate the impact of side effects on the daily lives of patients. Most Healthcare professionals described patients as doing well while on TKIs and side effects as tolerable.	
(Chuah et al. 2021)	Assessment of adherence to imatinib and health-related quality of life among patients with GIST: A cross-sectional study in an oncology clinic in Malaysia.	Imatinib	Cross-sectional study	Patients with unresectable and/or metastatic malignant GIST receiving imatinib treatment.	EORTC QLQ-C30, 10-item validated Medication Compliance Questionnaire	There was a statistically significant difference in the overall quality of life between adherent and non-adherent groups. Pertaining to the HRQoL scores in the functional dimension, only physical, emotional and cognitive functioning were significantly better among adherent patients. However, it is also important to note that there were non-significant trends for higher scores of adherent patients on all other scales in the functional dimension.	Population/ Outcome
(Fauske et al. 2020)	Striving towards normality in daily life: A qualitative study of patients living with a metastatic GIST in long-term clinical remission.	Imatinib, Sunitinib	Qualitative and exploratory study, semi-structured interviews	Patients living with metastatic GIST in long-term remission	NR	The participants described how living with metastatic GIST and its treatment posed challenges in relation to everyday life. They emphasised how this affected many facets of daily life, including family life, vocational life, and social life. In addition, living with uncertainty and an unsettled future proved burdensome for the participants. Many patients expressed how tiredness, including impaired memory, and physical challenges	Outcome

						were among the complaints that had a detrimental impact on their life. Half of the participants stated that uncertainty concerning drug resistance and the possibility of early death were severely challenging and, further, that they had to work hard to keep negative mental health issues at bay. Many participants reported struggling with lack of energy, eating restrictions, need for constant access to a toilet, and lack of desire or an inability to engage in sexual activity.	
(Banerjee et al. 2020)	Cost-effectiveness analysis of genetic testing and tailored first-line therapy for patients with metastatic GISTs	Imatinib, Sunitinib, BSC	Cost effectiveness analysis	Metastatic GIST	EQ-5D	Health utilities for a patient with metastatic GIST was defined as 0.935, while of 0.577 for metastatic GIST patients treated with BSC. Three opportunities for disease progression (first-line, second-line, and third-line treatments) were included in the model and were associated with health utility decrease of 0.12 for each disease progression. There was no QALY deduction associated with toxic effects from imatinib or sunitinib therapy based on clinical trial data that indicated equivalent QoL before and after treatment with either medication.	Study design
(Yoo et al. 2016) (RIGHT)	Impact of imatinib rechallenge on health-related quality of life in	Imatinib (400 mg) vs Placebo (PBO)	RCT, phase 3	Advanced GIST	EORTC QLQ-C30	At the time points of 4 and 8 weeks after study treatment, QoL parameters were compared after baseline adjustment using ANCOVA. After 4 weeks of study treatment,	Intervention

	patients with TKI-refractory GISTs: Sub-analysis of the PBO-controlled, randomised phase III trial (RIGHT)					no differences in EORTC-QLQ C-30 parameters were observed between the two groups after adjustment of baseline differences. At 8 weeks, there were no differences in global health status/QoL and functioning scales; however, several symptom scales showed significant differences at this time point; pain was better (p = 0.04) and nausea/vomiting, appetite loss, and diarrhoea were worse (p = 0.002, p = 0.01, and p = 0.04, respectively) in the imatinib group than in the PBO group. Despite a higher incidence of grade 3/4 fatigue in the imatinib group, the scores for fatigue in terms of EORTC QLQ-C30 did not differ between the two groups.	
(Blay et al. 2007)	Prospective multicentric randomized phase III study of imatinib in patients with advanced GISTs comparing interruption vs continuation of treatment beyond 1 year: The French sarcoma group	Interruption of imatinib until progression according to RECIST and then reintroduction of imatinib vs maintenance of imatinib until progression or intolerance	RCT, phase 3	Histologically proven metastatic GIST	EORTC QLQ-C30	The EORTC QLQ-C30 questionnaire was returned by 56 (57.1%) of the 98 assessable patients both at month 0 and 12. The EORTC QLQ-C30 scale global health status did not vary significantly in this series, with 20, 16, and 15 patients experiencing an improvement, worsening, or stable global health status. QoL was compared using the EORTC QLQ-C30 at 6 months; 29 (50%) of 58 patients returned the questionnaire at this stage. Although the numbers of patients in the two groups are limited, no significant differences were observed	Intervention

						regarding global health status, functional status, or symptoms scale.	
(Bauer 2014) (GRID)	HRQoL of patients with advanced GIST treated with regorafenib vs PBO in the phase III GRID trial	Regorafenib 160 mg daily + BSC vs placebo (PBO) + BSC	RCT, phase 3	Advanced GIST	EORTC QLQ-C30	Median time to discontinuation was comparable between treatments after removing disease progression from the definition. The responder analyses showed that a similar proportion of patients achieved an improvement in regorafenib vs PBO (QoL: 26.2% vs 25.4%; physical functioning: 18.0% vs 15.3%, respectively).	Outcome
(Ferguson et al. 2019)	Cognitive impairment and treatment effects among GIST survivors: Results of a large online survey	Imatinib (88.0%)	Prospective observational study	Adult GIST	FACT-Cog V3, PROMIS Short Forms 8a	A majority (63.9%) indicated significant negative QoL impact. FACT-Cog V3 did not correlate with emotional distress or fatigue, as in other cancer samples. Type of surgery, current use/non-use of imatinib or other therapy was not associated with FACT-Cog V3. However, GIST survivors ≥ 5 years post-diagnosis had significantly worse FACT-Cog V3 scores than survivors < 5 years postdiagnosis ($p < 0.05$).	Outcome
(Bouché et al. 2018) (EPIGIST)	EPigist: An observational real-life study on patients with metastatic GISTs receiving imatinib	Imatinib	Prospective observational study	Unresectable or metastatic KIT-positive GIST	SF-36, EORTC QLQ-C30	The QoL data using SF-36 and EORTC QLQ-C30 questionnaires were available for 110 patients at baseline, 92 patients after 6 months, 80 patients after 12 months, and 77 patients after 18 months. The patients' QoL remained generally stable during	Outcome

						imatinib therapy, with slight improvement in some mean SF-36 physical score and mental score). For the EORTC QLQ-C30, after 6 months of follow-up, 28.8% of the patients had improvement in the total score (10 points) of their QoL and 47.9% of patients remained stable (-10 to <10). After 12 months, 22.2% of patients had improved, 47.6% were stable; and after 18 months, 25.8% had improved, and 51.5% remained stable.	
(Chacon et al. 2018)	Quality of life and performance capacity in patients with breast cancer and patients with GIST	With or without systemic treatment	Prospective observation study	Metastatic and localised GIST	EORTC QLQ-C30, EORTC QLQ-BR23, RNLI, non-standardised questionnaire	QoL, on functional and symptomatic scales, in patients with metastatic GIST presented a score similar to its localised counterpart (77 versus 80). The household economic contribution was double for patients with localized disease compared to metastatic patients.	Outcome
(Wiener et al. 2012)	Gastrointestinal stromal tumour: Psychosocial characteristics and considerations	NR	Prospective observation study	GIST	Pre-Screening GIST Psychosocial Assessment form	Adult cohort: The majority of adult participants reported their physical health to be “good” (31%), “very good” (31%), or “excellent” (14%). 38% percent of adults reported experiencing pain at least a few days a week, over half of which report the pain interferes with their daily lives. Experiencing pain at least a few days per	Outcome

week was associated with changing moods quickly ($p<0.01$), difficulty getting along with family ($p<0.05$), crying easily or becoming easily upset ($p<0.05$), becoming easily distracted ($p<0.05$), getting anxious when separated from family ($p<0.001$), and concerns about body image and appearance ($p<0.01$). Whether or not a patient had their tumour completely resected was not associated with pain or mental health concerns. Emotionally, approximately one third of adult participants reported each of the following: crying easily or becoming easily upset (33%), having concerns about appearance or body image (33%), and feeling sad and withdrawn (30%). Although 40% reported having been treated by a mental health professional, only 13% indicated they are currently being treated. 52% percent of adults has ever taken psychiatric medications (27% currently). 43% percent of adults has taken anxiety medication (20% currently) and just under 1/3 has taken medication to treat depression (12% currently). Of the adults who have been prescribed psychotropic medication, 42% was prescribed these medications by their oncologist, 29% by a psychiatrist, and 10% by their primary care physician. Post-

						trauma symptoms were relatively prevalent in the adult cohort. The most frequently expressed need for services included: education about blood counts, treatment options and current research (77%), opportunity to meet other patients with the same illness (75%), nutritional guidance (67%), integrated complementary techniques for pain management (50%), exercise opportunities for self or family (48%), and interventions to reduce anxiety (47%).	
(Williams et al. 2014)	Symptoms in GISTs	NR	Prospective observational study	GIST	Single overall QoL question	Mean overall QoL rating was 7.8 (SD = 2.4).	Outcome
(Poort et al. 2016)	Prevalence, Impact, and Correlates of Severe Fatigue in Patients with GIST	3 groups based on their current treatment status: 1) treatment completed 2) treatment with curative intent, or 3) palliative treatment and BSC	Patient survey	Adult outpatients with localised or metastatic GIST	CIS-fatigue, SF-36 Health Survey, EORTC QLQ-C30, Fatigue Catastrophizing Scale, Self-Efficacy	Mean fatigue severity and the prevalence of severely fatigue did not differ significantly between the three groups, neither between patients receiving current TKIs or no TKIs. Severely fatigued patients reported significantly lower global QoL than non-severely fatigued patients and were more impaired on all EORTC-QLQ-C30 functional scales. More psychological distress, lower level of physical functioning, and currently receiving TKIs were	Outcome

					Scale, HADS	significantly associated with fatigue severity.	
(Custers et al. 2015)	Fear of progression in patients with GIST: Is extended lifetime related to the Sword of Damocles?	Metastatic (50%): Surgery and imatinib (n= 20) and Imatinib (n= 7), Local tumour (50%): Surgery and/or imatinib (n= 24) and Imatinib (n= 3)	Cross-sectional study	Localized or metastatic GIST - Disease phase at diagnosis: Local tumour 47 (87%) Metastatic 7 (13%)	EORTC QLQ-C30, HADS, IES, CWS, FCRI	Scores on the functional scales of the EORTC QLQ-C30 ranged from 76.9 to 84.3, indicating that the patients ' QoL was sufficient overall. Patients reported experiencing fatigue, diarrhoea, and insomnia. The mean score of 15.1 on the IES indicates that the patients had moderate problems adapting to the traumatic experience of cancer. Analysis of differences in QoL and distress between the two groups revealed medium to large clinical differences on the subscales role, emotional, cognitive, and social functioning and global health/quality of life, indicating that patients who experienced high levels of fear had a worse QoL. There were medium clinical differences on the symptom subscales insomnia, fatigue, pain, dyspnoea, and financial difficulties. Patients who experienced high fear of cancer recurrence reported significantly higher levels of general distress (50% vs. 15.4%; p <0.001) and cancer-specific distress (35.7% vs. 3.8%; p=0.001) than did patients who experienced low fear of cancer recurrence.	Outcome

(Langenberg et al. 2019)	Caregivers of patients receiving long-term treatment with a TKI for GIST: a cross-sectional assessment of their distress and burden*	TKIs	Cross-sectional study	GIST patients and caregivers	HADS, SSL-D, RAND-36, MMQ, SPPIC, Self-administered Comorbidity Questionnaire	Patients' general health was significantly different to normative comparatives for every dimension measured, except for mental health, which was comparable. The number of comorbidities affecting patients ranged from 0 (21.3%) to 6 (4.9%), with the most between 0 and 3 (85.2%); 78.7% had one or more comorbidity. Overall, the mean level of patients' general distress was 9.6 (SD 6.8; range 0–42) and 34% of patients experienced high levels of distress. Discrepancies in social support showed a mean score of 38.7 (SD 6.2; range 34–136). For marital satisfaction patients reported a mean score of 9.3 (SD 10.0; range 0–80).	Patient group / Outcome
(Chae et al. 2020)	Impact of l-carnitine on imatinib-related muscle cramps in patients with GIST	L-carnitine	Prospective observational study	Imatinib-related muscle cramps in patients with GIST	Questionnaire for the disturbance in basic activities of daily living (ADL), instrumental ADL, outdoor activity, or sleeping	Improvement in all aspects of the QoL after 3 months of L-carnitine treatment (interference in ADL, 73.2%–14.6%; interference in instrumental ADL, 73.2%–17.1%; sleeping disturbance, 78.0%–22.0%; limitations in outdoor activity, 68.3%–17.1%; all P< 0.001). When asked how they would rate their overall QoL disturbance, patients gave marks on 7 points in the median at the baseline, which went significantly down to 3 points after L-carnitine treatment ($p < 0.001$)	Intervention

Abbreviations: ADL: Activities of daily living, AE: Adverse event, ANCOVA: Analysis of covariance, BSC: Best supportive care, CIS-fatigue: Checklist Individual Strength Fatigue Severity scale, CWS: Cancer Worry Scale, C2DI: Day 1 of Cycle 2, DLQI: Dermatology Life Quality Index, EORTC-BR23: European Organization for Research and Treatment Breast cancer module, EORTC QLQ-C30: European Organization for Research and Treatment Quality of Life Questionnaire Core 30, EQ-5D, EuroQoL Five-Dimension (Five/Three-Level) questionnaire, FACT-Cog V3: Functional Assessment of Cancer Therapy-Cognitive Function-Version 3, FCRI: Fear of Cancer Recurrence Inventory, GIST: Gastrointestinal stromal tumours, HADS: Hospital Anxiety and Depression scale, HRQoL: Health related quality of life, HSUV: Health state utility values, IES: Impact of Event Scale, KIT: proto-oncogene c-KIT, L:Line of therapy, MCID: Minimal clinically important difference, MMQ: Maudsley Marital Questionnaire, N: Number, NR: Not reported, PBO: Placebo, PFS: Progression-free survival, PROMIS: Patient Reported Outcomes Measurement Information System, QALY: Quality adjusted life year, QoL: Quality of life, RCT: Randomised controlled trial, RNLI: Reintegration to Normal Living Index, RWE: Real world evidence, SD: Standard deviation; SF-36: 36-item short-form health survey, SSL-D: Social Support List – Discrepancies, SPPIC: Self-Perceived Pressure from Informal Care, TKI: tyrosine kinase inhibitor, UK: United Kingdom, VAS: Visual analogue scale.

I.1.3 Quality assessment and generalizability of estimates

Quality assessment is not available.

The included publications identified related to patients in multi-country studies, although they are not Danish specific. However, they are specific to patients with advanced GIST at late line treatment.

I.1.4 Unpublished data

No unpublished data was used in the SLR.

Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

In creating the health economic model for this application, further external literature was required. A systematic literature review was conducted to understand previous health economic analyses for advanced GIST. In addition, targeted desk research was conducted to identify relevant model inputs, for example from previous HTA reports for advanced GIST and Danish-specific health care unit costs.

J.1.1 Systematic search for health economic analyses for advanced GIST

A SLR of health economic analyses for advanced GIST was conducted. The process followed established practice and was comprised of the following core stages: definition of scope and agreement of search terms, implementation of searches and abstract review to inform included papers, and extraction and quality assessment of data. A search was conducted with its scope based on the PICOS framework as described in detail in Table 82 below.

Table 82 PICOS statement for the economic SLR in metastatic GIST

QoL PICOS	
Patient population	Patients diagnosed with advanced/metastatic or unresectable GIST At any line of therapy
Intervention and Comparators	No restriction
Outcome measures	Economic evaluation Budget impact analysis Burden of illness Measures of costs Measures of resource use
Study design	Budget impact analysis studies Resource use studies Cost/economic burden of illness studies Cost-benefit analysis Cost-effectiveness analysis

	Cost-minimisation analysis
	Cost-utility analysis
	Cost analysis
	Systematic reviews and meta-analyses (for cross-checking only)

Abbreviations: GIST: Gastrointestinal stromal tumours; PICOS: Patient, intervention, comparator, outcome, study design statement; QoL: Quality of life.

The key biomedical literature databases (Medical Literature Analysis and Retrieval System Online [MEDLINE®], Excerpta Medica Database [Embase®]) and Cochrane collaboration were consulted as described in Table 83. This is in accordance with the list of databases suggested by the HTA organisations, such as the CADTH, NICE, the PBAC, and the SMC. In addition, MEDLINE® was searched for Epub Ahead of Print, In-Process & Other Non-Indexed Citations to ensure that non-indexed citations would be retrieved.

Table 83 Bibliographic databases included in the health economic literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Ovid	2000-present	08.04.2024
Medline	Ovid	2000-present	08.04.2024
Cochrane	Ovid	2000-present	08.04.2024

Other sources were used to enrich the search. The bibliographies of systematic reviews and meta-analyses identified through database searches were used to identify key studies. Furthermore, bibliographies from selected studies were reviewed to identify studies relevant to the SLR. This process ensured that papers and articles not picked up in the initial search were included in the review.

In addition, desk research of the websites of the regulatory and HTA authorities in the UK (England and Scotland), Australia, and Canada was conducted. These other sources are detailed in see Table 84.

Table 84 Other sources included in the health economic literature search

Source name	Location/source	Search strategy	Date of search
Bibliographies	Systematic reviews and meta-analyses found through database searches	Review of all systematic review and meta-analysis bibliographies.	30.04.2024
NICE	www.nice.org.uk	Searches for relevant entries using key words in website-based search function.	30.04.2024

Source name	Location/source	Search strategy	Date of search
SMC	www.scottishmedicines.org.uk	Searches for relevant entries using key words in website-based search function.	30.04.2024
PBAC	www.pbac.pbs.gov.au	Searches for relevant entries using key words in website-based search function.	30.04.2024
CADTH	www.cadth.ca	Searches for relevant entries using key words in website-based search function.	30.04.2024

Abbreviations: NICE: National Institute fir Health and Care Excellence, SMC: Scottish Medicines Council, PBAC: Pharmaceutical Benefits Advisory Committee, CADTH, Canadian Agency for Drugs and Technologies in Health.

For conference abstracts (see Table 85) and ongoing clinical trials, the search terms “GIST”, “gastrointestinal stromal tumour” and “gastrointestinal stromal tumor” were used.

Table 85 Conference material included in the health economic literature search

Conference	Source of abstracts
American Society of Clinical Oncology (ASCO)	Conference proceedings
American Society of Clinical Oncology Gastrointestinal Symposium (ASCO GI)	Conference proceedings
European Society for Medical Oncology (ESMO)	Conference proceedings

J.1.1.1 Search strategies

The Ovid platform was used to conduct searches in the literature databases mentioned. Data were obtained by combining extensive lists of search terms for the indication, interventions, and study designs. The search strings included in the health economic literature search are detailed in Table 86, Table 87, and Table 88 below.

Table 86 Search strategy table for Medline in the health economic SLR

No.	Query	Results
#1	Gastrointestinal Stromal Tumors/	17677

Table 87 Search strategy table for Embase in the health economic SLR

No.	Query	Results
#1	gastrointestinal stromal tumor/	30038

Table 88 Search strategy table for all databases in the health economic SLR

No.	Query	Results
#1	(gastrointestinal stromal tumor$ or gastro-intestinal stromal tumor$ or gastro intestinal stromal tumor$ or gastrointestinal stromal tumour$ or gastro-intestinal stromal tumour$ or gastro intestinal stromal tumour$).ti,ab.	28482
#2	(gastrointestinal stromal neoplasm$ or gastro-intestinal stromal neoplasm$ or gastro intestinal stromal neoplasm$).ti,ab.	11
#3	(gastrointestinal stromal sarcoma$ or gastro-intestinal stromal sarcoma$ or gastro intestinal stromal sarcoma$).ti,ab.	39
#4	GIST.ti,ab.	23414
#5	exp "economic evaluation"/	471747
#6	economics/ or economic aspect/	393091
#7	Economics, Pharmaceutical/ or health economics/ or pharmacoeconomics/	51820
#8	cost-benefit analysis/ or "cost effectiveness analysis"/ or "cost minimization analysis"/ or "cost benefit analysis"/ or "cost utility analysis"/	450414
#9	((economic or human$) adj3 consequence$).ti,ab	24930
#10	(economic$ or pharmaco?economic$ or pharmaco economic$).ti,ab	1281234
#11	(cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$ or consequence$)).ti,ab	577294
#12	(CEA or CMA or CBA or CUA).ti,ab.	116311
#13	models, economic/ or economic model/	16477
#14	decision theory/ or decision trees/ or "decision tree"/	40036
#15	monte carlo method/	86664
#16	(econom$ model$).ti,ab.	31298
#17	markov$.ti,ab	86259

No.	Query	Results
#18	(discrete-event simulation$ or discrete event simulation$ or microsimulation$).ti,ab.	9258
#19	"monte carlo".ti,ab	137537
#20	(decision$ adj2 (tree$ or anal$ or model$)).ti,ab	105284
#21	("de novo" adj1 model$).ti,ab	533
#22	budgets/ or budget/	46388
#23	budget$.ti,ab.	114947
#24	"Costs and Cost Analysis"/ or cost/	120592
#25	"cost of illness"/	55508
#26	health care costs/ or "health care cost"/ or health expenditures/	306863
#27	cost$.ti,ab.	2192746
#28	Drug Utilization/ or "drug use"/	185127
#29	Health Resources/ or health care utilization/	274918
#30	((resource$ or health care or healthcare or health service$ or drug$ or medication$) adj4 (use$ or usage$ or utilit$ or utili#ation$)).ti,ab	1185868
#31	disease burden/	84602
#32	burden$.ti,ab.	917663
#33	(health technology assessment$ or health technolog$ or HTA).ti,ab.	37160

Of the 1914 articles identified through the OVID search, 362 were excluded after application of criteria limiting studies not involving humans, not being published in English, being published prior to the year 2000, and any duplicates. 1552 records remained for title/abstract review.

J.1.1.2 Systematic selection of literature

All 1552 publications were independently reviewed against the inclusion/exclusion criteria summarised in Table 89 below. All literature included by the reviewer at the end of this stage were retained for Step 2. Publications included after abstract review (from Step 1) were obtained for a full review of the text. All papers included after the full-text review were retained for data extraction. A record was kept of papers excluded at this stage along with a clear justification for their exclusion. Two independent reviewers screened all

citations and full-text articles and any discrepancies in their decisions were resolved by a third independent reviewer. Data from included studies (from Step 2) were extracted into a pre-defined Excel-based template, ensuring that data were extracted uniformly and were comparable across studies. Two analysts independently extracted data and their results were checked and reconciled by a third independent analyst.

Table 89 Inclusion and exclusion criteria for the health economic systematic literature review

Element	Inclusion	Exclusion
Patient population	Patients diagnosed with advanced/metastatic or unresectable GIST At any line of therapy	Non-human Adjuvant/neoadjuvant setting
Intervention and Comparators	No restriction	Studies not including at least one of the interventions listed in the inclusion criteria
Outcome measures	Economic evaluation Budget impact analysis Burden of illness Measures of costs Measures of resource use	Studies not including at least one of the outcomes listed in the inclusion criteria
Study design	Budget impact analysis studies Resource use studies Cost/economic burden of illness studies Cost-benefit analysis Cost-effectiveness analysis Cost-minimisation analysis Cost-utility analysis Cost analysis Systematic reviews and meta-analyses (for cross-checking only)	Reviews Editorials Notes/comments/letters
Restrictions	English language Year limitation: 2000-current	Non-English language studies

Abbreviations: GIST: gastro-intestinal stromal tumour.

Of the 1552 records which were selected for abstract review, 95 records were selected full-text review, after screening by title/abstract. Following full-text review, a total of 34 records from 31 original studies were selected for data extraction in the economic SLR.

Details of the included and excluded studies are presented in the PRISMA flow diagram in Figure 40.

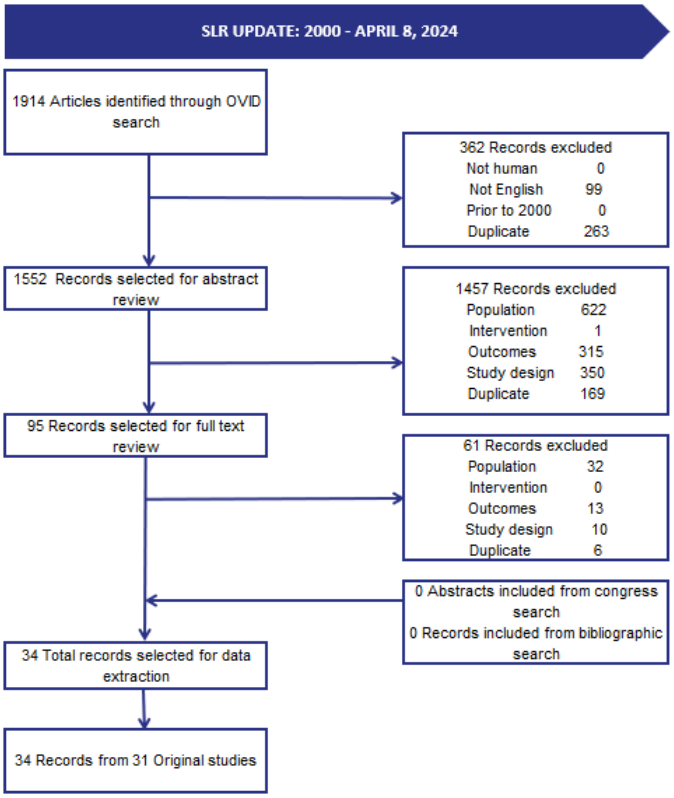


Figure 40 PRISMA flow diagram for the health economic literature review

J.1.1.2.1 SLR findings regarding health economic analyses for GIST

SLR results regarding health economic analysis in GIST are presented in Table 90 below. These were not directly included in the application but to increase understanding of how to best analyse the cost-effectiveness of a new treatment for this disease.

Table 90 Results from the Systematic Literature Review for Health Economics

Reference	Title	Interventions	Population	Summary of model
(Liao et al. 2021) INVICTUS	Cost-effectiveness analysis of fourth- or further-Line ripretinib in advanced GIST.	Ripretinib vs PBO	Patients with advanced GIST	Model Type: Markov model, Health States: progression-free, progression, death, Cycle Lengths: 28 days, Perspective: payer, Horizon: Lifetime, Discount Rate: 3% per annum costs and health benefits.
(Zhang et al. 2023) GRID	PCN52 Cost-effectiveness analysis of the third-line treatment of regorafenib for metastatic or unresectable GIST in China.	Regorafenib + BSC vs PBO + BSC	Patients with metastatic or unresectable GIST in China.	Model Type: Partitioned survival model, Health States: 3 states, Cycle Lengths: NR, Perspective: NR, Horizon: Lifetime, Discount Rate: NR
(Rui et al. 2022)	Cost-effectiveness analysis of third line pazopanib vs regorafenib for metastatic or unresectable GIST in China.	Pazopanib vs. Regorafenib	Patients who had metastatic or unresectable GISTs, with the previous failure of at least two drugs, including both imatinib and sunitinib.	Model Type: Three-state partitioned survival model, Health States: progression-free, progression and death, Cycle Lengths: NR, Perspective: Health care system, Horizon: Lifetime (10 years), Discount Rate: NR
(Pitcher et al. 2016) GRID	Cost-effectiveness analysis of regorafenib in GIST in England using crossover adjustment methods	Regorafenib + BSC vs BSC	Metastatic/ unresectable GIST	Model Type: partitioned survival model, Health States: 3 - progression-free, progressed, dead, Cycle Length: NR, Perspective: English healthcare payer, Horizon: Lifetime (40 years), Discount Rate: 3.5% on costs and effects
(Banerjee et al. 2020)	Cost-effectiveness analysis of genetic testing and tailored first-line therapy for patients with metastatic GIST.	Avapritinib	Unresectable/metastatic GISTs harbouring a PDGFRA	Model Type: Budget impact model (claims based), Health States: NR, Cycle Length: NR, Perspective: US managed care health plan, Horizon: 3 years,

Reference	Title	Interventions	Population	Summary of model
			exon 18 variant, including PDGFRA D842V variants	Discount Rate: None owing to the short time horizon.
(Proudman et al. 2020a)	Financial implications of avapritinib for treatment of unresectable GIST in patients with a PDGFRA exon 18 variant or after 3 previous therapies in a hypothetical US health plan.	Avapritinib	Unresectable/metastatic GISTs harbouring a PDGFRA exon 18 variant, including PDGFRA D842V variants	Model Type: Budget impact model (claims based), Health States: NR, Cycle Length: NR, Perspective: US managed care health plan, Horizon: 3 years, Discount Rate: None owing to the short time horizon.
(Farid et al. 2020)	Treatment of GIST of the rectum requiring abdominoperineal resection following neoadjuvant imatinib: A cost-effectiveness analysis.	Continued imatinib until progression vs Surgical resection with upfront abdominoperineal resection	Rectal GIST requiring abdominoperineal resection following neoadjuvant imatinib	Model Type: Markov, Health States: 12 including resection at 1st year, resection at 2nd year, resection at 3rd year and beyond, 1st local recurrence following upfront abdominoperineal resection, Patients receiving the second strategy continued imatinib, Patients undergoing abdominoperineal resection following local progression on continued imatinib or subsequently salvage surgery following 1st local recurrence after abdominoperineal resection on continued imatinib, Distant recurrence, 1st progression in metastatic disease, 2nd progression in metastatic disease, 3rd progression in metastatic disease, death. Cycle Length: 1 year, Perspective: Healthcare payer, Horizon: 20 years, Discount Rate: 3% annually for costs and health outcomes

Reference	Title	Interventions	Population	Summary of model
(Bond et al. 2009)	Sunitinib for the treatment of gastrointestinal stromal tumours: a critique of the submission from Pfizer	Sunitinib vs PBO	Unresectable and/or metastatic GIST after failure of imatinib	Model Type: Markov model, Health States: 3- progression-free survival, progressive disease, death, Cycle Length: NR, Perspective: Healthcare payer and Personal social services perspective, Horizon: NR, Discount Rate: NR
(Hislop et al. 2011)	Clinical effectiveness and cost-effectiveness of imatinib dose escalation for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours that have progressed on treatment at a dose of 400 mg/day: A systematic review and economic evaluation.	Imatinib	Unresectable and/or metastatic GIST	Model Type: Markov model, Health States: 7 care pathways with BSC, imatinib 600-stable, imatinib 800-stable, sunitinib-stable, progress, failed treatment BSC, death, Cycle Length: 1 month, Perspective: Healthcare payer perspective, Horizon: 10 years, Discount Rate: 3.5% on cost and benefit
(Wilson et al. 2005)	Imatinib for the treatment of patients with unresectable and/or metastatic gastrointestinal stromal tumours: Systematic review and economic evaluation.	Imatinib vs control	Unresectable and/or metastatic GIST	Model Type: state-transition model, Health States: Control group: 2- progressive disease, death, imatinib group: 3 - imatinib treatment, progressive disease, death, Cycle Length: 4 weeks, Perspective: UK healthcare payer, Horizon: 10 years, Discount Rate: 6% for costs and 1.5% for health benefit
(Centanni and Friberg 2020)	Model-Based Biomarker Selection for Dose Individualization of Tyrosine-Kinase Inhibitors.	Sunitinib (Fixed dosing (control) vs therapeutic drug monitoring/management -based dosing vs absolute	1,000 virtual individuals with metastatic and/or unresectable GIST	Model Type: partitioned survival model, Health States: 3- progression-free, progressed, dead, Cycle Length: NR, Perspective: English healthcare payer, Horizon: lifetime (40 years), Discount Rate: 3.5% on costs and effects

Reference	Title	Interventions	Population	Summary of model
		change in neutrophil count -based dosing vs biomarker-based dosing		
(Zuidema et al. 2019)	Optimizing the dose in patients treated with imatinib as first-line treatment for gastrointestinal stromal tumours: A cost-effectiveness study	Imatinib therapeutic drug monitoring/management -guided dosing vs imatinib fixed dosing	GIST	Model Type: Markov model, Health States: Seven care pathways with BSC, imatinib 600-stable, imatinib 800-stable, sunitinib-stable, progress, failed treatment BSC, death, Cycle Length: 1 month, Perspective: Healthcare payer perspective, Horizon: 10 years, Discount Rate: 3.5% on cost and benefit
(Tamoschus et al. 2017)	Cost-Effectiveness Analysis of Regorafenib for Gastrointestinal Stromal Tumour (GIST) in Germany.	Regorafenib vs Imatinib rechallenge	Metastatic and/or unresectable GIST after treatment failure with at least imatinib and sunitinib	Model Type: Markov model Health States: 3 - progression-free survival, progressive disease, death, Cycle Length: NR, Perspective: Healthcare and Personal social services payer perspective, Horizon: NR, Discount Rate: NR
(Nerich et al. 2017)	Cost-Effectiveness Analysis of Tyrosine Kinase Inhibitors for Patients with Advanced Gastrointestinal Stromal Tumors.	Strategy 1: 1L imatinib 400 mg/day followed by BSC. - Strategy 2: 1L imatinib 400 mg/day, followed	Advanced GIST	Model Type: state-transition model, Health States: Control group: 2 - progressive disease, death, imatinib group: 3 - imatinib treatment, progressive disease, death, Cycle Length: 4 weeks, Perspective: English healthcare payer, Horizon: 10 years, Discount Rate: 6% for costs and 1.5% for health benefit

Reference	Title	Interventions	Population	Summary of model
		by 2L imatinib 800 mg/day, followed by BSC - Strategy 3: 1L imatinib 400 mg/day, followed by 2L sunitinib 50 mg/day for 4 consecutive weeks followed by a 2-weeks off period, followed by BSC - Strategy 4: 1L imatinib 400 mg/day, followed by 2L imatinib 800 mg/day + 3L sunitinib 50 mg/day for 4 consecutive weeks followed by a 2-weeks off period, followed by BSC.		
(Sanz-Granda et al. 2015)	Estimation of the threshold price of regorafenib in the treatment of unresectable and/or metastatic GIST after	Regorafenib vs BSC	Unresectable and/or metastatic GIST	Model Type: probabilistic cost-utility Markov model, Health States: 3 - stable, progression, death, Cycle Length: NR, Perspective: Spanish

Reference	Title	Interventions	Population	Summary of model
	failure on imatinib and sunitinib in Spain: Cost-utility analysis			healthcare payer perspective, Horizon: lifetime, Discount Rate: 3% on costs and benefits
(Paz-Ares et al. 2008)	Cost-effectiveness analysis of sunitinib in patients with metastatic and/or unresectable GIST after progression or intolerance with imatinib.	Sunitinib vs BSC	Metastatic and/or unresectable GIST after progression or intolerance with imatinib	Model Type: partitioned survival model, Health States: 3 - progression-free, progressed, dead, Cycle Length: NR, Perspective: English healthcare payer, Horizon: lifetime (40 years), Discount Rate: 3.5% on costs and effects
(Deger et al. 2015)	The cost-effectiveness of regorafenib in the treatment of metastatic/inoperable GIST in Turkey.	Regorafenib vs standard care	Metastatic/inoperable GIST	Model Type: Markov model, Health States: Seven care pathways with BSC, imatinib 600-stable, imatinib 800-stable, sunitinib-stable, progress, failed treatment BSC, death, Cycle Length: 1 month, Perspective: healthcare payer perspective, Horizon: 10 years, Discount Rate: 3.5% on cost and benefit
(El Ouagari 2008)	Cost-effectiveness of imatinib in the treatment of advanced GIST: Canadian perspective.	Imatinib vs No treatment	Unresectable/metastatic GIST	Model Type: Markov model, Health States: 3 - progression-free survival, progressive disease, death, Cycle Length: NR, Perspective: Healthcare and Personal social services payer perspective, Horizon: NR, Discount Rate: NR
(Chabot et al. 2008)	The challenge of conducting pharmacoeconomic evaluations in oncology using crossover trials: the example of sunitinib for GIST.	Sunitinib vs BSC	GIST intolerant or resistant to imatinib	Model Type: state-transition model, Health States: Control group: 2 -progressive disease, death, imatinib group: 3 - imatinib treatment, progressive disease, death, Cycle Length: 4 weeks, Perspective:

Reference	Title	Interventions	Population	Summary of model
				UK healthcare payer, Horizon: 10 years, Discount Rate: 6% for costs and 1.5% for health benefit
(Mabasa et al. 2008)	Verification of imatinib cost-effectiveness in advanced GIST in British Columbia (VINCE-BC study).	Imatinib vs Control (historical)	Advanced GIST	Model Type: partitioned survival model, Health States:3 - progression-free, progressed, dead, Cycle Length: NR, Perspective: English healthcare payer, Horizon: Lifetime (40 years), Discount Rate: 3.5% on costs and effects
(Huse et al. 2007)	Cost effectiveness of imatinib mesylate in the treatment of advanced GIST.	Imatinib mesylate vs No treatment (palliative and supportive care only)	Advanced GIST	Model Type: Markov model, Health States: Seven care pathways with BSC, imatinib 600-stable, imatinib 800-stable, sunitinib-stable, progress, failed treatment BSC, death, Cycle Length: 1 month, Perspective: Healthcare payer perspective, Horizon: 10 years, Discount Rate: 3.5% on cost and benefit
(Ren et al. 2015)	Cost-effectiveness of sunitinib as second-line treatment for GIST in China.	Sunitinib 50 mg/day vs Imatinib 600 mg/day, Imatinib 800 mg/day or BSC	Metastatic and/or unresectable GIST after progression or intolerance with imatinib	Model Type: Markov model, Health States: 3 progression-free survival, progressive disease, death, Cycle Length: NR, Perspective: Healthcare and Personal social services payer perspective, Horizon: NR, Discount Rate: NR
(Contreras-Hernández et al. 2008)	A pharmaco-economic analysis of second-line treatment with imatinib or sunitinib in patients with advanced GIST	Sunitinib vs palliative care vs	Advanced GIST	Model Type: state-transition model, Health States: Control group: 2 - progressive disease, death, imatinib group: 3 -imatinib treatment, progressive

Reference	Title	Interventions	Population	Summary of model
		high doses of imatinib		disease, death, Cycle Length: 4 weeks, Perspective: UK healthcare payer perspective, Horizon: 10 years, Discount Rate: 6% for costs and 1.5% for health benefit
(Teich et al. 2009)	Economic evaluation of sunitinib vs. imatinib in second line for GIST in Brazil.	Sunitinib vs Imatinib or BSC	GIST whose tumour continued to progress	Model Type: partitioned survival model, Health States: 3-progression-free, progressed, dead, Cycle Length: NR, Perspective: healthcare payer perspective, Horizon: Lifetime (40 years), Discount Rate: 3.5% on costs and effects.
(Proudman et al. 2020b)	PCN84 budget impact analysis of ayvakit (avapritinib) in patients with GIST and a pdgfra exon 18 mutation.	Avapritinib	Adult patients with unresectable or metastatic GIST with a PDGFRA exon 18 mutation, including a D842V mutation	Model Type: budget impact model, Health States: NR, Cycle Length: NR, Perspective: US health plan (commercial, Medicare, Medicaid, or a mix), Horizon: 3 years, Discount Rate: no discounting on costs
(Hansen et al. 2019)	PCN107 budget impact analysis of larotrectinib for 8 tumors in the United States.	Larotrectinib	Patients with neurotrophic tyrosine receptor kinase fusion in colorectal, non-small cell lung, melanoma, thyroid, gastrointestinal stromal tumour, infantile fibrosarcoma, soft tissue sarcoma, and salivary gland cancer.	Model Type: budget impact model, Health States: NR, Cycle Length: NR, Perspective: US health plan, Horizon: flexible time horizon, Discount Rate: NR

Reference	Title	Interventions	Population	Summary of model
(Chung et al. 2023)	The characteristics and outcomes of gastrointestinal stromal tumor with and without liver metastasis.	NR	Patients with GIST, secondary malignant neoplasm, and secondary malignant neoplasm of the liver and intrahepatic bile duct.	NR
(Gelderblom et al. 2023) INTRIGUE	Patient reported outcomes and tolerability in patients receiving ripretinib vs sunitinib after imatinib treatment in INTRIGUE: A phase 3 open-label study.	Ripretinib vs Sunitinib	Patients ≥ 18 years of age with histologic diagnosis of advanced GIST after treatment with imatinib	NR
(Seal et al. 2014)	Treatment patterns and cost of care for patients with GIST treated with imatinib	Imatinib, sunitinib	GIST	NR
(Datar and Khanna 2012)	Inpatient burden of GIST in the United States	NR	GIST	NR
(Halpern et al. 2009)	Costs and utilization associated with imatinib adherence in patients with chronic myeloid leukemia or GIST.	Imatinib	Patients with chronic myeloid leukaemia or GIST	Model Type: NR, Health States: NR, Cycle Length: NR, Perspective: NR, Horizon: NR, Discount Rate: NR
(Look Hong et al. 2014)	The economic impact of cytoreductive surgery and tyrosine kinase inhibitor therapy in the treatment of advanced GIST: a Markov chain decision analysis.	Surgery + Imatinib or Sunitinib	Metastatic/recurrent GIST	Model Type: Markov chain cohort simulation model, Health States: NR, Cycle Length: 3 months, Perspective: Government/payer perspective, Horizon: 2 years, Discount Rate: 3% on costs

Reference	Title	Interventions	Population	Summary of model
(Fleck et al. 2012)	Cost of illness of localized and metastatic GIST.	Imatinib, Sunitinib	Localised/metastatic GIST	Model Type: NR, Health States: NR, Cycle Length: NR, Perspective: French Public Health Insurance perspective, Horizon: NR, Discount Rate: NR
(Deger et al. 2015)	The cost-of-disease of metastatic/Inoperable GIST in turkey: An expert panel approach for estimation of costs.	NR	Metastatic/inoperable GIST	Model Type: NR, Health States: NR, Cycle Length: NR, Perspective: Turkish payer perspective, Horizon: NR, Discount Rate: NR

Abbreviations: BSC: Best supportive care, GIST: Gastrointestinal stromal tumour, L: Line (of therapy), NR: Not reported, PBO: Placebo, PDGFRA: Platelet-derived growth factor reception A, UK: United Kingdom, US: United States of America.

J.1.1.2.2 SLR and wider desk research findings on utility data

Studies reporting utility data were identified through the HRQoL SLR (Appendix I), economic SLR (Current appendix) including the HTA review, and bibliographic search of their references. There were two sources of utility values:

- Values collected from patients directly (involved few studies, which tended to be older studies with small sample sizes and did not provide values for all health states relevant to the metastatic GIST economic models)
- Values mapped from collected HRQoL studies.

In total, 18 publications reporting utility data were identified through the HRQoL SLR, economic SLR, HTA review, and bibliographic search of their references:

- Three studies in the HRQoL SLR (Poole et al. 2015, Zolic et al. 2015, Zhang et al. 2023).
- Nine studies in the economic SLR (Hislop et al. 2011, Wilson et al. 2005, Paz-Ares et al. 2008, Chabot et al. 2008, Banerjee et al. 2020, Farid et al. 2020, Liao et al. 2021, Rui et al. 2022, Jones et al. 2022).
- Five HTA appraisals (NICE 2009, NICE 2023, Scottish Medicines Agency (SMC), Pharmaceutical Benefits Advisory Committee (PBAC) 2015, CADTH Reimbursement Review 2022).
- One study was identified through bibliographic search of the references of selected studies (Demetri et al. 2006). No utility data were reported in the publication by Demetri et al. 2006. The values were extracted from clinicaltrials.gov.

Published utility values in GIST by health state are presented in Table 91.

Table 91 Published utility values by health state from HRQoL and Health economic SLR

Reported Health State	Population	Utility Value	Data Source	Reference
		Point Estimate		
First-line advanced GIST				
Progressive disease in 1L	Unresectable and/or metastatic GIST (1L)	0.875	ECOG category mapped to EQ-5D	(Wilson et al. 2005)
Progressive disease in 1L & 2L	Metastatic GIST	0.935	Measured EQ-5D	(Banerjee et al. 2020)
Progressive disease in 1L & 2L	Metastatic GIST patients treated with BSC	0.577	Measured EQ-5D	(Banerjee et al. 2020)
Recurrence-free health state post abdominoperineal resection	Metastatic GIST	0.83	Standard gamble interviews	(Farid et al. 2020)
Recurrence-free health state on continued imatinib until progression	Metastatic GIST	0.935	ECOG category mapped to EQ-5D	(Farid et al. 2020)
GIST recurrence	Metastatic GIST	0.748	NR	(Farid et al. 2020)
GIST 1st progression	Metastatic GIST	0.712	Measured EQ-5D	(Farid et al. 2020)
Imatinib-treated	Unresectable and/or metastatic GIST (1L)	0.935	ECOG category mapped to EQ-5D	(Wilson et al. 2005)
Imatinib 800mg/day	Unresectable and/or metastatic GIST whose disease had progressed on 400 mg/day	0.935	ECOG category mapped to EQ-5D	(Hislop et al. 2011)
Imatinib 600mg/day	Unresectable and/or metastatic GIST whose disease had	0.935	ECOG category mapped to EQ-5D	(Hislop et al. 2011)

	progressed on 400 mg/day			
Progressive disease in 1L	Unresectable and/or metastatic GIST (1L)	0.875	ECOG category mapped to EQ-5D	(Wilson et al. 2005)
Second-line advanced GIST				
GIST 2nd progression	Metastatic GIST	0.712	Assumption based on Chabot et al. 2008	(Farid et al. 2020)
Progression in 2L	GIST intolerant or resistant to imatinib	0.577	measured EQ-5D	(Chabot et al. 2008)
Progressive disease in 2L – lower-level values for sensitivity analysis	Unresectable and/or metastatic GIST whose disease had progressed on 400 mg/day	0.52	ECOG category mapped to EQ-5D	(Hislop et al. 2011)
Progressive disease health state in 2L (both arms, sunitinib+BSC and PBO+BSC)	Unresectable and/or metastatic malignant GIST after failure of imatinib mesylate treatment due to resistance or intolerance	0.577	Measured EQ-5D	(NICE 2009)
Disease progression state in 2L	Imatinib-resistant or intolerant metastatic and/or unresectable GIST	0.577	Measured EQ-5D	(Paz-Ares et al. 2008)
Progression-free health state in 2L (sunitinib + BSC arm)	Unresectable and/or metastatic malignant GIST after failure of imatinib mesylate treatment due to resistance or intolerance	0.731	Measured EQ-5D	(NICE 2009)
Progression-free health state in 2L (PBO + BSC arm)	Unresectable and/or metastatic malignant GIST after failure of imatinib mesylate treatment due to resistance or intolerance	0.781	Measured EQ-5D	(NICE 2009)

Sunitinib treatment	Unresectable and/or metastatic GIST whose disease had progressed on 400 mg/day	0.935	Measured EQ-5D	(Hislop et al. 2011)
No progression: during the 4 weeks on sunitinib treatment (2L)	GIST intolerant or resistant to imatinib	0.712	measured EQ-5D	(Chabot et al. 2008)
No progression: utility improvement during the 2 weeks off sunitinib treatment (2L)	GIST intolerant or resistant to imatinib	0.081	measured EQ-5D	(Chabot et al. 2008)
Sunitinib – no progression, during the 4 weeks with the treatment of each cycle in 2L	Imatinib-resistant or intolerant metastatic and/or unresectable GIST	0.712	Measured EQ-5D	(Paz-Ares et al. 2008)
Sunitinib – no progression, during the 2 weeks without the treatment of each cycle (rest weeks) in 2L	Imatinib-resistant or intolerant metastatic and/or unresectable GIST	0.769	Measured EQ-5D	(Paz-Ares et al. 2008)
Sunitinib - Cycle 4 Day 1	Imatinib-resistant advanced GIST	0	Measured EQ-5D	(Demetri et al. 2006)
Sunitinib - Cycle 3 Day 28	Imatinib-resistant advanced GIST	-0.036	Measured EQ-5D	(Demetri et al. 2006)
Sunitinib - Cycle 3 Day 1	Imatinib-resistant advanced GIST	0	Measured EQ-5D	(Demetri et al. 2006)
Sunitinib - Cycle 2 Day 28	Imatinib-resistant advanced GIST	-0.017	Measured EQ-5D	(Demetri et al. 2006)
Sunitinib - Cycle 2 Day 1	Imatinib-resistant advanced GIST	0	Measured EQ-5D	(Demetri et al. 2006)
Sunitinib - Cycle 1 Day 28	Imatinib-resistant advanced GIST	0	Measured EQ-5D	(Demetri et al. 2006)
BSC – no progression in 2L	Imatinib-resistant or intolerant metastatic and/or unresectable GIST	0.781	Measured EQ-5D	(Paz-Ares et al. 2008)

No progression: BSC (2L)	GIST intolerant or resistant to imatinib	0.781	Measured EQ-5D	(Chabot et al. 2008)
PBO - Cycle 4 Day 1	Imatinib-resistant advanced GIST (2L)	0.059	Measured EQ-5D	(Demetri et al. 2006)
PBO - Cycle 3 Day 28	Imatinib-resistant advanced GIST (2L)	0	Measured EQ-5D	(Demetri et al. 2006)
PBO - Cycle 3 Day 1	Imatinib-resistant advanced GIST (2L)	0	Measured EQ-5D	(Demetri et al. 2006)
PBO - Cycle 2 Day 28	Imatinib-resistant advanced GIST (2L)	0	Measured EQ-5D	(Demetri et al. 2006)
PBO - Cycle 2 Day 1	Imatinib-resistant advanced GIST (2L)	0	Measured EQ-5D	(Demetri et al. 2006)
PBO - Cycle 1 Day 28	Imatinib-resistant advanced GIST (2L)	0	Measured EQ-5D	(Demetri et al. 2006)
At study initiation	Imatinib-resistant or intolerant metastatic and/or unresectable GIST	0.785	Assumption for both groups	(Paz-Ares et al. 2008)
Third-line advanced GIST				
GIST 3rd progression	Metastatic GIST	0.712	Assumption based on Chabot et al. 2008	(Farid et al. 2020)
Progression free	Recurrent/metastatic GIST 3L+	0.8	Measured EQ-5D	(Zhang et al. 2023)
Progressive disease	Recurrent/metastatic GIST 3L+	0.7	Measured EQ-5D	(Zhang et al. 2023)
Advanced GIST with first progression-free state in 3L	Advanced GIST (3L)	0.767	Measured EQ-5D	(Liao et al. 2021)
Advanced GIST with first post-progression state in 3L	Advanced GIST (3L)	0.647	Measured EQ-5D	(Liao et al. 2021)
Death	Advanced GIST (3L)	0	Measured EQ-5D	(Liao et al. 2021)
Progression-free state - Pazopanib	Advanced GIST (3L)	0.78	Measured EQ-5D	(Rui et al. 2022)

Progression-free state - Regorafenib	Advanced GIST (3L)	0.779	Measured EQ-5D	(Rui et al. 2022)
Progressive disease	Advanced GIST (3L)	0.647	Measured EQ-5D	(Rui et al. 2022)
Disease progression in 3L (at baseline, day 1 of cycle 1)	Advanced GIST (3L)	0.793	Measured EQ-5D	(Poole et al. 2015)
Advanced GIST without disease progression in 3L (at baseline, day 1 of cycle 1)	Advanced GIST (3L)	0.76	Measured EQ-5D	(Poole et al. 2015)
Progression-free state in 3L (regorafenib or PBO)	GIST patients who must have previously failed or be intolerant to imatinib mesylate and sunitinib	0.767	Measured EQ-5D	(Pharmaceutical Benefits Advisory Committee (PBAC) 2015)
Progression-free state in 3L	Unresectable or metastatic GIST who progressed on or are intolerant to prior treatment with imatinib and sunitinib	0.74	Measured EQ-5D	(Scottish Medicines Agency (SMC))
Progression-free state in 3L (regorafenib or PBO)	Metastatic and/or unresectable GIST (3L)	0.872	Experience-based health states (EQ-5D) reported by patients with GIST in the GRID trial combined with utility weights derived from a Swedish population	(Zolic et al. 2015)
Progression-free state in 3L (regorafenib or PBO)	Metastatic and/or unresectable GIST (3L)	0.85	Simplest repeated measures model, not including variables for treatment effect	(Zolic et al. 2015)

Advanced GIST with first progression-free state in 3L	Advanced GIST (3L)	0.767	Measured EQ-5D	(Poole et al. 2015)
Progressed disease state in 3L	Unresectable or metastatic GIST who progressed on or are intolerant to prior treatment with imatinib and sunitinib	0.68	Measured EQ-5D	(Scottish Medicines Agency (SMC))
Post-progression state in 3L (regorafenib or PBO)	GIST patients who must have previously failed or be intolerant to imatinib mesylate and sunitinib	0.647	Measured EQ-5D	(Pharmaceutical Benefits Advisory Committee (PBAC) 2015)
Progression-free state in 3L (regorafenib or PBO)	Metastatic and/or unresectable GIST (3L)	0.806	Experience-based health states (EQ-5D) reported by patients with GIST in the GRID trial combined with utility weights derived from a Swedish population	(Zolic et al. 2015)
Progression-free state in 3L (regorafenib or PBO)	Metastatic and/or unresectable GIST (3L)	0.814	Simplest repeated measures model, not including variables for treatment effect	(Zolic et al. 2015)
Advanced GIST with first post-progression state in 3L	Advanced GIST (3L)	0.647	Measured EQ-5D	(Poole et al. 2015)
Regorafenib 160 mg + BSC (at baseline, day 1 of cycle 1)	Advanced GIST (3L)	0.779	Measured EQ-5D	(Poole et al. 2015)
Advanced GIST with 3L (at baseline, day 1 of cycle 1)	Advanced GIST (3L)	0.755	Measured EQ-5D	(Poole et al. 2015)

Advanced GIST with 4L+ (at baseline, day 1 of cycle 1)	Advanced GIST (3L)	0.787	Measured EQ-5D	(Poole et al. 2015)
PBO + BSC (at baseline, day 1 of cycle 1)	Advanced GIST (3L)	0.751	Measured EQ-5D	(Poole et al. 2015)
Fourth-line advanced GIST				
Post-progression state	Unresectable or metastatic GIST	0.647	Measured EQ-5D	(NICE 2023)
Baseline with ripretinib	Advanced GIST (4L+)	0.7606	Measured EQ-5D	(CADTH Reimbursement Review 2022)
Baseline with PBO	Advanced GIST (4L+)	0.7547	Measured EQ-5D	(CADTH Reimbursement Review 2022)
Cycle 2 day 1 with ripretinib	Advanced GIST (4L+)	0.7762	Measured EQ-5D	(CADTH Reimbursement Review 2022)
Cycle 2 day 1 with PBO	Advanced GIST (4L+)	0.7545	Measured EQ-5D	(CADTH Reimbursement Review 2022)
Advanced GIST with progression-free state in 4L+	Advanced GIST (4L+)	0.817	Measured EQ-5D	(CADTH Reimbursement Review 2022)
Advanced GIST with progression-disease state in 4L+	Advanced GIST (4L+)	0.807	Measured EQ-5D	(CADTH Reimbursement Review 2022)
Advanced GIST with progression-free state in 4L+	Advanced GIST (4L+)	0.712	Measured EQ-5D	(CADTH Reimbursement Review 2022)
Advanced GIST with progression-disease state in 4L+	Advanced GIST (4L+)	0.577	Measured EQ-5D	(CADTH Reimbursement Review 2022)
Disutilities due to Grade 3 and 4 AEs	Advanced GIST (4L+)	-0.069 to -0.085	Measured EQ-5D	(CADTH Reimbursement Review 2022)
Advanced GIST with progression-free	Advanced GIST (4L+)	0.75	Measured EQ-5D	(Jones et al. 2022)

state in 4L+ treated with ripretinib				
Advanced GIST with progression-disease state in 4L+ treated with ripretinib	Advanced GIST (4L+)	0.75	Measured EQ-5D	(Jones et al. 2022)
Advanced GIST with progression-free state in 4L+ treated with PBO	Advanced GIST (4L+)	0.73	Measured EQ-5D	(Jones et al. 2022)
Advanced GIST with progression-disease state in 4L+ treated with PBO	Advanced GIST (4L+)	0.71	Measured EQ-5D	(Jones et al. 2022)
Advanced GIST with progression-free state	Advanced GIST	0.81	Measured EQ-5D	(Jones et al. 2022)
Advanced GIST with progression-disease state	Advanced GIST	0.67	Measured EQ-5D	(Jones et al. 2022)

Abbreviations: AEs: Adverse events, BSC: best supportive care, ECOG: Eastern Cooperative Oncology Group, EQ-5D: European Quality of Life group five-item questionnaire, GIST: Gastrointestinal stromal tumorus, HRQoL: Health-related quality of life, L: Line (of therapy),NR: not reported, PBO: Placebo, SLR: Systematic literature review.

J.1.1.3 Quality assessment and generalizability of estimates

Quality assessment of the relevant cost-effectiveness studies that were published in abstracts or full-text was conducted using the Drummond checklist. This is available upon request.

J.1.1.4 Unpublished data

No unpublished data was used in the SLR.

J.1.2 Targeted literature search for model inputs

In addition, targeted literature searches for inputs required for the health economic model were conducted. These included desk research of the relevant HTA authorities in the Nordic countries (Denmark Sweden, Norway), NICE, as well as specific data from Statistics Denmark and for Danish unit costs.

Table 92 Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
NICE	https://www.nice.org.uk/guidance/ta523	Desk research	30.04.2024
TLV	https://www.tlv.se/	Desk research	27.05.2024
NoMA	https://www.dmp.no/en	Desk research	27.05.2024
DMC	https://medicinraadet.dk/	Desk research	27.05.2024
Statistics Denmark	https://www.dst.dk/en	Desk research	27.05.2024
Sundhedsdatastyrelsen	https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/takster-drg/takster-2024	Desk research	28.06.2024
Danish Medicines Agency	https://www.medicinpriser.dk/	Desk research	28.06.2024
Laeger.dk	https://laeger.dk/	Desk research	28.06.2024

Abbreviations: DMC: Danish Medicines Council, NoMA: Norwegian Medical Products Agency, TLV: Tandvårds- & läkemedelsförmånsverket / Swedish Dental and Pharmaceutical Benefits Agency.

Disutility values in the health economic model for the three included AEs were identified in NICE HTA reports for GIST (TA730) and colorectal cancer (TA439: review of TA176 and partial review TA240) (NICE 2017a, NICE 2021). From these reports, reference list scanning identified the original utility source (Doyle et al. 2008, Harrow et al. 2011). Where

appropriate the disutility values were scaled to EQ-5D as reported in Hoyle et al. (Hoyle et al. 2013).

Danish-specific unit costs were sourced from appropriate sources according to the Danish Medicines Council's method guide (Danish Medicines Council 2021b).

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