

Single Technology Appraisal

Ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments (review of TA881) [ID6496]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments (review of TA881) [ID6496]

Contents:

The following documents are made available to stakeholders:

Access the [final scope](#) and [final stakeholder list](#) on the NICE website.

- 1. Company submission** from Deciphera
- 2. Company summary of information for patients (SIP)** from Deciphera
- 3. Clarification questions and company responses**
 - a. Clarification response
 - b. B9 Clarification response
 - c. Company addendum – updated base case
- 4. Patient group, professional group and NHS organisation submissions** from:
 - a. GIST Cancer UK
 - b. PAWS-GIST
 - c. Sarcoma UK
- 5. Expert personal perspectives** from:
 - a. Dr Charlotte Benson, Consultant Medical Oncologist – clinical expert, nominated by PAWS-GIST
 - b. Jayne Bressington, GIST Patient advocate / Patient Director PAWS-GIST – patient expert nominated by PAWS-GIST
 - c. Fiona Newton, Special Volunteer (Research) – patient expert nominated by GIST Cancer UK
- 6. External Assessment Report** prepared by School of Health and Related Research (SchARR)
 - a. EAG report
 - b. EAG report addendum
- 7. External Assessment Report – factual accuracy check**

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Single technology appraisal

Ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments (review of TA881) [ID6496]

Company evidence submission

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Company evidence submission template for ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments (review of TA881) [ID6496]

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Abbreviations

1L	First Line
2L	Second Line
3L	Third Line
4L	Fourth Line
AIC	Akaike Information Criterion
ANCOVA	Analysis of Covariance Models
ASCO	American Society of Clinical Oncology
AE	Adverse Event
BIC	Bayesian Information Criterion
BICR	Blinded Independent Central Review
BID	Twice a Day
BNF	British National Formulary
BSC	Best Supportive Care
BSG	British Sarcoma Group
CADTH	Canadian Agency for Drugs and Technologies in Health
CAR	Chimeric Antigen Receptor
CEA	Cost-Effectiveness Analysis
CI	Confidence Interval
CR	Complete Response
CrI	Credible Interval
CT	Computed Tomography
CTCAE v5.0	Common Terminology Criteria for Adverse Events Version 5.0
CUA	Cost-Utility Analysis
DSU	Decision Support Unit
EAG	Evidence Appraisal Group

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ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EQ5D5L	EuroQol 5 Dimensions 5 Levels
EQVAS	EuroQol Visual Analogue Scale
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items
FDA	Food and Drug Administration
GIST	Gastrointestinal Stromal Tumour
HR	Hazard Ratio
HRG	Healthcare Resource Group
HRQoL	Health-Related Quality of Life
HSE	Health Survey for England
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
IPCW	Inverse Probability of Censoring Weights
IPDE	Intra-Patient Dose Escalation
IQR	Interquartile Range
ITT	Intention-To-Treat
KIT	KIT Proto-Oncogene Receptor Tyrosine Kinase
LYG	Life Years Gained
m/r	Modified Release
MIMS	Monthly Index of Medical Specialities
mRECIST v1.1	Modified Response Evaluation Criteria in Solid Tumours Version 1.1
MRI	Magnetic Resonance Imaging
MHRA	Medicines and Healthcare products Regulatory Agency
MMRM	Mixed Model of Repeated Measures

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MVH	Measurement and Valuation of Health
NE	Not Estimable
NICE	National Institute for Health and Care Excellence
NHB	Net Health Benefit
NR	Not Reported
OD	Once a Day
OR	Objective Response
ORR	Objective Response Rate
OS	Overall Survival
OWSA	One Way Sensitivity Analysis
PAS	Patient Access Scheme
PASLU	Patient Access Scheme Liaison Unit
PD	Progressive Disease
PDGFRA	Platelet-Derived Growth Factor Receptor Alpha
PF	Progression Free
PFS	Progression-Free Survival
PFSA	Probabilistic Sensitivity Analysis
PH	Proportional Hazards
PR	Partial Response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-Reported Outcome
PSM	Partitioned Survival Model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-Adjusted Life Year
QC	Quality Control

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QD	Once Daily
QDS	Four Times a Day
QoL	Quality of Life
RCT	Randomised Controlled Trial
RPSFT	Rank Preserving Structural Failure Time
SAE	Serious Adverse Event
SD	Stable Disease
SD	Standard Deviation
SE	Standard Error
SLR	Systematic Literature Review
SmPC	Summary of Product Characteristics
SoC	Standard of Care
STS	Soft Tissue Sarcoma
TDS	Three Times a Day
TIE2	Tyrosine Kinase with Immunoglobulin-like and EGF-like Domains 2
TKI	Tyrosine Kinase Inhibitor
TTD	Time to Treatment Discontinuation
TTP	Time to Progression
TUDD	Time Until Definitive Deterioration
VAS	Visual Analogue Scale
VEGFR2	Vascular Endothelial Growth Factor Receptor 2
WTP	Willingness to Pay

1 Decision problem, description of the technology and clinical care pathway

1.1 Ripretinib overview and positioning in ≥fourth-line advanced GIST

Gastrointestinal stromal tumour (GIST) is a rare, life-threatening sarcoma that affects the gastrointestinal tract; it commonly develops in the stomach and small intestine (60-70%) but can occur anywhere in the gastrointestinal tract.¹⁻³ The median age at presentation is 60-65 years, with an incidence of 1.5 out of every 100,000 people.⁴ GIST is a highly complex disease, with the potential for many mutations to drive treatment-resistance and disease progression. Central drivers of tumour development are mutations in the KIT proto-oncogene receptor tyrosine kinase (KIT) and/or platelet-derived growth factor receptor alpha (PDGFRA).

There is no cure for advanced GIST and there remains a significant unmet need for effective treatment options. In the UK, imatinib is the standard first-line (1L) treatment for patients with advanced disease.^{4,5} Upon progression or intolerance to imatinib, the standard second-line (2L) treatment is sunitinib.^{4,6} For patients whose disease progresses on or fails to respond to imatinib and sunitinib, regorafenib is the standard third-line (3L) treatment option.^{4,7} Patients often develop secondary drug-resistance mutations and, as a result, generally progress rapidly through the available treatment options, receiving only moderate clinical benefit.⁸⁻¹³ The median progression free survival (PFS) for patients receiving 3L regorafenib is 4.8 months, and the objective response rate (ORR) is 4.5%.^{8,9,14}

UK clinical practice guidelines from the British Sarcoma Group (BSG) recommend ripretinib as the preferred option for fourth-line treatment in patients with inoperable, progressive, or metastatic GIST after treatment with imatinib, sunitinib, and regorafenib. However, ripretinib is not broadly available to patients in the UK.⁴ Current fourth-line treatment, and the most appropriate comparator for ripretinib, is best supportive care (BSC), which includes medication for symptomatic management, for example analgesics, laxatives, and antiemetics.^{15,16} Patients having BSC have poor

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survival and health-related quality of life (HRQoL).¹⁷⁻¹⁹ Clinician and patient expert testimony both state that there is a high unmet need for an effective fourth-line treatment that broadly targets KIT and PDGFRA mutation-positive and wild-type GIST and has the potential to extend life and improve patient HRQoL.²⁰

Ripretinib is a once-daily oral treatment and is the only switch-control tyrosine kinase inhibitor (TKI) specifically designed to broadly inhibit wild type and mutated KIT and PDGFRA kinases, with a unique dual mechanism of action.^{21,22}

In a randomised, placebo-controlled trial (INVICTUS) in patients with advanced GIST previously treated with three or more TKIs, ripretinib significantly improved median PFS compared with placebo (6.3 months vs 1.0 month), thereby reducing the risk of disease progression or death by 85% (HR 0.15; 95% confidence interval [95% CI] 0.09 to 0.25; $p < 0.0001$).¹⁵

Ripretinib achieved a clinically meaningful 64% reduction in the risk of death (HR 0.36; 95% CI 0.21 to 0.62), leading to an 8.5-month improvement in median overall survival (OS) vs placebo in the primary analysis.¹⁵ By the January 2021 data cut-off, this had increased to a 11.9-month improvement in median OS over placebo, 18.2 months vs 6.3 months respectively (HR 0.41).²³ As such, ripretinib nearly tripled OS for these patients, after an initial median follow up of 6.3 months and an additional 19 months of follow-up after the initial analysis.²³ Importantly, ripretinib showed durable, clinically meaningful disease control.²³ Despite advanced disease, patients receiving ripretinib maintained HRQoL and function over approximately 8 months, while the same measures declined sharply for patients receiving placebo after just 1 month.¹⁶ Ripretinib was well-tolerated and demonstrated an acceptable safety profile.^{15,23}

1.2 Decision problem

The submission covers the technology's full marketing authorisation for this indication. The decision problem that is addressed in this submission is presented in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with advanced GIST who have received prior treatment with three or more kinase inhibitors, including imatinib	As per scope	N/A
Intervention	Ripretinib	As per scope	N/A
Comparator(s)	Established clinical management.	Best supportive care (BSC)	The specific comparator should be BSC, where BSC is established clinical management of 4th line ($\geq 4L$) advanced GIST.
Outcomes	The outcome measures to be considered include: • overall survival • progression free survival • response rate (including partial response rate and duration of response) • stable disease • adverse effects of treatment • health-related quality of life.	As per scope	N/A
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be	As per scope	N/A

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	sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.		
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • people whose disease progressed after previous treatment with tyrosine kinase inhibitors • people whose disease is resistant or intolerant to tyrosine kinase inhibitors	Subgroups not considered	There is no differentiation in clinical guidelines or clinical practice based on subgroups for the 3 prior lines of therapy in advanced GIST; as such the INVICTUS trial protocol did not make this distinction
Special considerations including issues related to equity or equality	None identified.	There are no special considerations relating to issues of equity or equality.	N/A

1.3 Description of the technology being evaluated

Table 2 presents a brief description of ripretinib for treating adult patients with advanced GIST who have received prior treatment with three or more kinase inhibitors, including imatinib. The Summary of product characteristics (SmPC) can be found in Appendix A.

Table 2: Technology being evaluated

UK approved name and brand name	Ripretinib (Qinlock®)
Mechanism of action	Ripretinib is a switch-control TKI that inhibits KIT proto-oncogene receptor tyrosine kinase and PDGFRA kinase, including wild-type, primary, and secondary mutations. Ripretinib also inhibits other kinases in vitro, such as PDGFRB, TIE2, VEGFR2, and BRAF.
Marketing authorisation/CE mark status	MHRA approved ripretinib on 21st December 2021.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Ripretinib is indicated for the treatment of adult patients with advanced GIST who have received prior treatment with three or more kinase inhibitors, including imatinib. Contraindications are hypersensitivity to the active substance or to any of the excipients listed in the SmPC.
Method of administration and dosage	Ripretinib is an oral therapy. The recommended (licensed) dose is 150 mg ripretinib (three 50 mg tablets) taken once daily at the same time each day with or without food. If the patient misses a dose of ripretinib within 8 hours of the time it is usually taken, the patient should be instructed to take it as soon as possible and then take the next dose at the regularly scheduled time. If a patient misses a dose by more than 8 hours of the time it is usually taken, the patient should be instructed not to take the missed dose and simply resume the usual dosing schedule on the following day. In case of vomiting after ripretinib administration, the patient should not take a replacement dose and should resume the dosing schedule the next day at the usual time.

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	Treatment with ripretinib should continue as long as benefit is observed or until unacceptable toxicity. Dose interruptions or dose reductions may be required based on individual safety and tolerability. The recommended dose reduction for adverse reactions is 100 mg orally, once daily.
Additional tests or investigations	Patients with or a history of high blood pressure will be monitored during ripretinib treatment and may administer medicine to treat high blood pressure, if needed. For patients with a history of heart conditions, patients will have additional tests to assess heart function prior to and during ripretinib treatment. Specifically, ejection fraction should be assessed by echocardiogram or multiple-gated acquisition (MUGA) scan prior to initiating ripretinib and during treatment, as clinically indicated. Ripretinib should be permanently discontinued for Grade 3 or 4 left ventricular systolic dysfunction.²⁴ Ripretinib may increase the risk of some types of skin cancers. Dermatological evaluations should be performed when initiating ripretinib and routinely during treatment. Suspicious skin lesions should be managed with excision and dermatopathological evaluation. Ripretinib should be continued at the same dose.²⁴
List price and average cost of a course of treatment	£18,400 list price per 30-day supply, based on a dose of 150 mg once daily (3 x 50 mg tablets). As an oral treatment, ripretinib is VAT exempt.
Patient access scheme (if applicable)	A patient access scheme has been submitted in the form of a simple discount on the list price of ripretinib.

1.4 Health condition and position of the technology in the treatment pathway

1.4.1 Disease overview

GIST is a rare, life-threatening and heterogeneous subset of soft tissue sarcoma (STS), and the most common mesenchymal tumour of the gastrointestinal (GI) tract. Although occurring anywhere in the GI tract, GIST most frequently develops in the stomach (60% to 70% of cases) or small intestine (25% to 35% of cases).^{1-3,25} The colon and rectum are involved in approximately 4% to 5% of cases.^{1-3,25}

GIST is a highly complex disease, developing in specialised interstitial cells of Cajal within the GI tract and primarily driven by mutations in the KIT transmembrane receptor tyrosine kinase and the related receptor tyrosine kinase, platelet-derived growth factor receptor alpha (PDGFRA).^{26,27} Approximately 80% of GIST has primary mutations in KIT, and 5% to 10% have a mutation in homologous PDGFRA.^{1,28,29}

Most primary KIT mutations involve a single mutation at diagnosis.¹ However secondary mutations can develop over time in response to treatment with targeted TKI therapies, leading to treatment resistance.^{28,30} These acquired secondary resistance mutations are seen in up to two thirds of GIST cases that progress after TKI treatment. As a result, the disease is heterogenous and the patient may have multiple mutations.^{28,31,32} There is, therefore, an unmet need for a treatment that is able to target both primary and secondary KIT and PDGFRA resistance mutations.

Clinical presentation and burden of disease

The median age at GIST presentation is 60-65 years, with an incidence of 1.5 out of every 100,000 people.⁴ There are approximately 900-1,000 new cases of GIST per year in the UK; of these, approximately 173 will progress to fourth-line treatment for advanced GIST.^{4,8,33-36}

The clinical presentation of GIST can vary based on the tumour size and site.^{3,37} Symptoms of advanced disease include gastrointestinal bleeding and anaemia, whilst larger tumours may present with abdominal pain/discomfort, obstruction and a
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palpable mass. Some patients may have non-specific systemic symptoms such as extreme tiredness, weight loss, night sweats and fever.⁴

Patients with fourth-line advanced GIST have particularly poor survival outcomes. Median overall survival (OS) for patients with advanced GIST receiving BSC after 3 prior lines of therapy with TKIs can be as short as 1.8 months, although this is a worst-case scenario.¹⁵ When clinicians were consulted on the anticipated survival of patients with ≥ 4 L advanced GIST if only treated with BSC, they anticipated OS to be 2 to 3 months.³⁸

The humanistic impact of advanced GIST is substantial. Patient HRQoL deteriorates severely as the disease progresses, with a significant reduction in cognitive and social functioning.¹⁶ Over half of patients with advanced GIST experience high levels of fear of disease progression, often related to the lack of later-line therapeutic options, leading to significant psychological distress.³⁹ The psychological burden often leads to patients with GIST having difficulties in making and maintaining relationships, as well as experiencing body image concerns, low mood and depressive symptoms.⁴⁰ Furthermore, the toxicity of currently available later-line therapies makes them difficult to tolerate. For example, results from the phase 3 randomised controlled trial (RCT) GRID showed that regorafenib is not associated with any statistically significant benefit in HRQoL. This was attributed to the severe adverse events associated with regorafenib dosing.⁴¹ Many patients therefore require dose adjustment or treatment interruption, which can contribute to rapid progression through the available therapeutic options.^{42,43} This is then accentuated by an increased financial burden and the result this has on a patient's well-being.⁴⁴

In addition to the impact on patients, caring for someone with GIST also imposes a significant emotional, financial, and social burden. Carers often take on numerous responsibilities, such as providing emotional support, accompanying patients when leaving their home and on medical and non-medical appointments, and assisting with communication and travel. According to the National Sarcoma Survey 2020, more than half of GIST carers had to stop working or studying, either temporarily or permanently.⁴⁵

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1.4.2 Clinical management of advanced GIST and place of ripretinib in the treatment pathway

There is no cure for advanced GIST. Approximately half of patients present with metastatic or unresectable GIST at diagnosis and around 40% to 90% of patients who have had surgery develop subsequent postoperative recurrence or metastasis.^{35,36} Targeted therapy with TKIs is the standard of care for metastatic or unresectable GIST. Conventional chemotherapy and radiotherapy are not effective in this advanced patient population.^{39,46,47}

In patients with metastatic or unresectable disease, imatinib is the 1L standard treatment in the UK.^{4,5} Disease progression after imatinib treatment occurs mostly due to primary resistance or secondary KIT mutation. If progression or imatinib intolerance is confirmed, the standard 2L treatment is sunitinib. Most patients will again relapse within 6 months to 1 year due to additional or alternative secondary mutations in KIT, or due to multiple different KIT mutations occurring in different areas of the tumour.¹¹ In addition, some patients with imatinib-resistant disease have primary resistance to sunitinib due to the specific secondary mutation(s) that arise during imatinib treatment.⁸ Regorafenib is regarded as standard therapy for the 3L treatment of patients whose disease has progressed on or failed to respond to imatinib and sunitinib.⁷

Patients with advanced GIST progress quickly through available therapies. For patients who progress on 1L treatment with imatinib, subsequent lines of TKI therapy have moderate clinical benefit due to the development of secondary drug-resistance mutations.⁸ Response rates are generally lower in later lines of treatment and median PFS becomes shorter.^{8,9,14} Median PFS for patients receiving 3L regorafenib is 4.8 months, and the ORR is 4.5%.^{8,9,14} This is primarily as the three available TKIs only block a subset of clinically relevant secondary resistance mutations.^{9,10,12} Therefore, given the heterogeneous nature of KIT and PDGFRA mutations in advanced GIST, it is desirable to use a treatment that inhibits as many mutations as possible.⁴⁸

There is no established standard of care in the UK for patients who have received prior treatment with three or more kinase inhibitors, including imatinib. Importantly, Company evidence submission template for ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments (review of TA881) [ID6496]

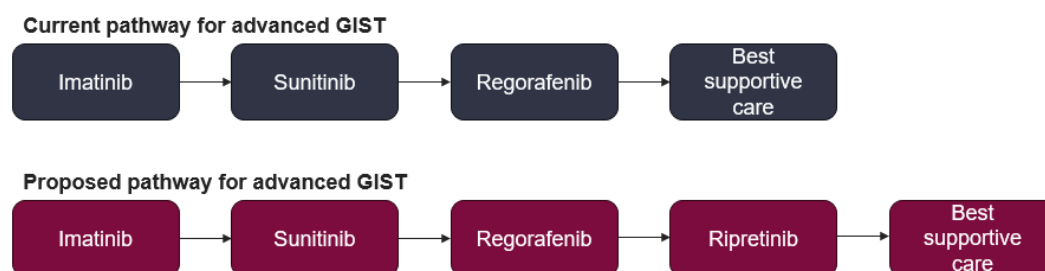
clinicians and patient experts have highlighted the substantial unmet need for a treatment that is effective in patients with TKI resistance.²⁰ Current treatment, and the most appropriate comparator for ripretinib, is BSC which involves symptomatic management using analgesics, laxatives, and antiemetics.¹⁷⁻¹⁹

In clinical practice, regorafenib may continue to be used after disease progression because of the lack of alternative treatment options.^{4,7,18,38,49} However, clinical experts noted that post-progression regorafenib is a last resort after seeking relevant clinical trials or other therapies via compassionate use.^{18,20} This is because it only has benefits for a limited time and is associated with toxicities that often outweigh any potential clinical benefits after progression.¹⁸

Ripretinib is currently recommended as a later line treatment option for patients with advanced/metastatic GIST in British (BSG) and European (ESMO) clinical practice guidance.^{4,49} Prior to this, the recommended approach for patients with advanced/metastatic GIST who had progressed through 3 previous lines of therapy was BSC and enrolment onto clinical trials.^{49,50}

There remains a substantial unmet medical need for a treatment which provides broad inhibition of KIT and PDGFRA kinase activity, including wild-type and secondary drug-resistance mutations, to extend life and improve patient HRQoL.^{48,51} It is therefore proposed that the place of ripretinib would be in the fourth-line of treatment, alongside BSC, as shown in Figure 1.

Figure 1: Current and proposed clinical pathway for patients with advanced GIST in the UK



Abbreviations: GIST: Gastrointestinal stromal tumours

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1.5 Equality considerations

There are no known equality issues relating to the use of ripretinib for treating advanced GIST after previous treatment with three or more TKIs.

2 Clinical effectiveness

2.1 Identification and selection of relevant studies

Clinical and HRQoL systematic literature reviews (SLR) were originally conducted from January 2000 to July 2020 to identify the clinical, HRQoL and economic evidence relevant to ripretinib, respectively. Specifically, the clinical SLR was conducted in the target population of patients with advanced (unresectable or metastatic) GIST to assess the relative efficacy and safety of ripretinib and comparators in fourth-line or later. The SLRs were subsequently updated five times including July 2021 (Ovid search conducted on June 24, 2021), March 2022 (Ovid search conducted on March 21, 2022), May 2023 (Ovid search conducted on May 17, 2023), April 2024 (Ovid search conducted on April 8, 2024) and March 2025 (Ovid search conducted on March 10, 2025).

For the clinical SLR, a total of 1,574 records were identified using the Ovid platform on March 10, 2025. Of these, 114 records were selected for full-text review, after screening by title/abstract. Overall, following a full-text review and the addition of studies from congress, bibliographic search, and clinicaltrials.gov, a total of 39 records from 2 original studies were selected for data extraction in the clinical SLR.

Please see Appendix B and F for details on the clinical and HRQoL SLR methodology and process used to select the clinical and HRQoL evidence for ripretinib in the fourth and later-line setting ($\geq 4L$) for the treatment of advanced GIST, including Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagrams.

2.2 List of relevant clinical effectiveness evidence

The clinical SLR identified 39 reports, 15 of which were relevant to this submission (Table 3). Of these publications, 10 were regarding the original pivotal phase 3, double-blind, placebo-controlled, randomised trial (INVICTUS), which provided direct head-to-head evidence on the clinical benefits of ripretinib vs placebo in patients with advanced unresectable or metastatic GIST who had progressed following imatinib, sunitinib, and regorafenib. The remaining 24 were deemed not relevant as the

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intervention of the study was not ripretinib and/or they did not contain a relevant comparator.

Results of a phase 2 single-arm, open-label study (NCT04282980) of ripretinib 150 mg once daily in adult patients with advanced GIST who had progressed on three or more prior kinase inhibitors (n=39) are reported in two publications. Efficacy and safety results were broadly consistent with the INVICTUS trial and are not discussed further in this submission.^{52,53}

The clinical SLR also identified two publications, relating to the phase 1, non-randomised study (NCT02571036) of ripretinib that included a dose escalation and expansion phase of patients with GIST in the 2L, 3L, and $\geq$ 4L setting who were treated with ripretinib at the 150 mg QD dose.^{54,55} Efficacy and safety results were broadly consistent with the INVICTUS trial and are not discussed further in this submission.

The HRQoL SLR identified four further relevant publications reporting HRQoL analyses of INVICTUS, in addition to Blay et al., 2020,¹⁵ Becker et al., 2021,⁵⁶ Reichardt et al., 2021,⁵⁷ and Bauer et al., 2023.⁵⁸ These include a key publication by Schoffski et al., 2022¹⁶ and three posters: two were presented at the 2020 ASCO Annual Meeting by Heinrich et al., 2020 and George et al., 2020 and one was presented at ISPOR 2022 by Jones et al., 2022.⁵⁹⁻⁶¹

Table 3: Trials and key reports presented in the submission in order of publication (INVICTUS)

Report/citation
Clinical SLR
von Mehren M, Serrano C, Bauer S, et al. INVICTUS: A phase III, interventional, double-blind, placebo-controlled study to assess the safety and efficacy of ripretinib as $\geq$ 4th-line therapy in patients with advanced gastrointestinal stromal tumors (GIST) who have received treatment with prior anticancer therapies (NCT03353753). <i>Annals of Oncology</i> . 2019;30(Supplement 5):v925-v926. Presentation at the 44 th ESMO Congress. Spain ⁶²

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Blay JY, Serrano C, Heinrich MC, et al. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial. <i>The Lancet Oncology</i> . 2020;21(7):923–34 ¹⁵
Correction to <i>Lancet Oncol</i> 2020;21:923–34. <i>The Lancet Oncology</i> . 21(7) (pp e341), 2020. Date of Publication: July 2020 ⁶³
Serrano C, Heinrich MC, George S, et al. Efficacy and safety of ripretinib as ≥4th-line therapy for patients with gastrointestinal stromal tumor (GIST) following crossover from placebo: Analyses from INVICTUS [Presentation]. Presentation at the ESMO World Congress on Gastrointestinal Cancer Virtual Meeting; 2020 July 1-4 ⁶⁴
Zalcberg JR, Heinrich M, George S, et al. Clinical benefit with ripretinib as ≥ 4th line treatment in patients with advanced gastrointestinal stromal tumors (GIST): Update from the phase III INVICTUS study. <i>Annals of Oncology</i> . 2020;31(Supplement 4):S973-S974. Presentation at ESMO Virtual Congress 2020 ⁶⁵
Zalcberg JR, Heinrich MC, George S, et al. Clinical Benefit of Ripretinib Dose Escalation After Disease Progression in Advanced Gastrointestinal Stromal Tumor: An Analysis of the INVICTUS Study. <i>The Oncologist</i> . 2021;9999:1-11 ⁶⁶
von Mehren M, Heinrich MC, George S, Zalcberg JR, Bauer S, Gelderblom H, Schöffski P, Serrano C, Jones RL, Attia S, D'Amato G. 1540P Ripretinib as ≥ 4th-line treatment in patients with advanced gastrointestinal stromal tumor: Long-term update from the phase III INVICTUS study. <i>Annals of Oncology</i> . 2021 Sep 1;32:S1120-1. ²³
Reichardt P, Heinrich M, George S, Zalcberg J.R, Bauer S, Gelderblom H, Schöffski P, Serrano C, Jones R.L, Attia S, D'Amato G, Chi P, Lacouture M.E, Cha E, Meade J.N, Ruiz-Soto R, Blay J.-Y, Von Mehren M. Safety profile of ripretinib, including impact of alopecia, and palmar-plantar erythrodysesthesia syndrome (ppes) on patient-reported outcomes (PROS), in ≥ fourth-line advanced gastrointestinal stromal tumors (Gist): Analyses from invictus. <i>Oncology Research and Treatment</i> . Conference: Jahrestagung der Deutschen, Österreichischen und Schweizerischen Gesellschaften für Hamatologie und Medizinische Onkologie. Berlin Germany. 44(SUPPL 2) (pp 186-187), 2021. Date of Publication: 2021. ⁵⁷
Becker C, Harrow B, Heinrich MC, Schöffski P, Serrano C, Vincenzi B, Blay JY. POSB342 Time Until Definitive Deterioration (TUDD) in Patient Reported Outcomes (PROS) in a Phase 3 Trial for Ripretinib in 4L Patients with Gastrointestinal Stromal Tumour (GIST). <i>Value in Health</i> . 2022 Jan 1;25(1):S227. ⁵⁶

Bauer S., Heinrich M.C., George S., Zalcberg J.R., Gelderblom H., Schoffski P., Serrano C., Jones R.L., Attia S., D'amato G., Chi P., Reichardt P., Becker C.C., Meade J., Ruiz-Soto R., Von Mehren M., Blay J.-Y. Quality of life and self-reported function with ripretinib in ≥ 4th-line therapy for patients with gastrointestinal stromal tumors: Analyses from INVICTUS. Oncology Research and Treatment. Conference: Jahrestagung der Deutschen, Österreichischen und Schweizerischen Gesellschaften für Hamatologie und Medizinische. Hamburg Germany. 46(Supplement 5) (pp 153-154), 2023. Date of Publication: October 2023. ⁵⁸
Li J, Cai S, Zhou Y, et al. Efficacy and Safety of Ripretinib in Chinese Patients with Advanced Gastrointestinal Stromal Tumors as a Fourth- or Later-Line Therapy: A Multicenter, Single-Arm, Open-Label Phase II Study. Clinical Cancer Research. 2022;28(16):3425-3432. doi:10.1158/1078-0432.CCR-22-0196⁵²
Li J, Zhang J, Zhang Y, et al. Efficacy and safety of ripretinib vs sunitinib in patients with advanced gastrointestinal stromal tumor previously treated with imatinib: A phase 2, multicenter, randomized, open-label study in China European Journal of Cancer. 2024;196doi:10.1016/j.ejca.2023.113439⁵³
ClinicalTrials.gov. NCT04282980 A Multicenter Phase 2, Single-Arm Open-Label Study of DCC-2618 to Assess Efficacy, Safety, and Pharmacokinetics In Patients With Advanced Gastrointestinal Stromal Tumors Who Have Progressed On Prior Anticancer Therapies. Accessed 28/04/2025, https://clinicaltrials.gov/study/NCT04282980?term=NCT04282980&rank=1⁶⁷
HRQoL SLR
Heinrich MC, George S, Zalcberg J, et al. Quality of life (QoL) and self-reported function with ripretinib in ≥ 4th line therapy for patients with gastrointestinal stromal tumors (GIST): Analyses from INVICTUS [Poster 423]. Poster presented at the 2020 ASCO Annual Virtual Meeting; 2020 May 29-31 ⁵⁹
George S, Heinrich MC, Zalcberg J, et al. Safety profile of ripretinib, including impact of alopecia and palmar-plantar erythrodysesthesia syndrome (PPES) on patient reported outcomes (PROs), in ≥ 4th line advanced gastrointestinal stromal tumors (GIST): Analyses from INVICTUS [Poster 427]. Poster presented at the 2020 ASCO Annual Virtual Meeting; 2020 May 29-31 ⁶¹
Jones RL, Blay JY, Chi P, Bauer S, Gelderblom H, Shen L, He YL, Heinrich MC, Schöffski P, Zalcberg JR, Harrow B. P61 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. Value in Health. 2022 Dec 1;25(12):S14-5. ⁶⁰
Schöffski P, George S, Heinrich MC, Zalcberg JR, Bauer S, Gelderblom H, Serrano C, Jones RL, Attia S, D'Amato G, Chi P. 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. 2022 Dec 13;22(1):1302. ¹⁶
Internal reports
Deciphera Pharmaceuticals, LLC. 2019. Data on File: Phase 3, interventional, double-blind, placebo-controlled study to assess the safety and efficacy of DCC-2618 in patients with advanced gastrointestinal stromal tumors who have received treatment with prior anticancer therapies (INVICTUS) [Clinical Study Report] ¹⁹
Deciphera Pharmaceuticals, LLC. 2019. Data on File: Statistical Analysis Plan; Protocol No. DCC-2618-03-001. A Phase 3, Interventional, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of DCC-2618 In Patients with Advanced Gastrointestinal Stromal Tumors who have Received Treatment with Prior Anticancer Therapies [Final Version 2.0] ⁶⁸

Details of the phase 3 INVICTUS RCT identified in SLR searches are provided in Table 4.

Table 4: Clinical effectiveness evidence

Study	INVICTUS (NCT03353753)
Study design	Phase 3, multicentre, double-blind, placebo-controlled, randomised trial
Population	Patients with advanced (metastatic or unresectable) GIST aged ≥18 years, ECOG PS of 0-2, and with disease progression on imatinib, sunitinib, and regorafenib (fourth-line or later)
Intervention(s)	Ripretinib + BSC
Comparator(s)	Placebo + BSC
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A
Reported outcomes specified in the decision problem	PFS, OS, Response rate (including partial response rate, stable disease and duration of response), HRQoL and AEs
All other reported outcomes	Time to progression, Time to best response, Time to treatment discontinuation (post-hoc)

Abbreviations: AE – Adverse event; BSC – Best supportive care; ECOG PS – Eastern Cooperative Oncology Group Performance Status; GIST – Gastrointestinal stromal tumour; HRQoL – Health-related quality-of-life; N/A – Not applicable; OS – Overall survival; PFS – Progression-free survival

Although outside of the remit of the SLR, real-world data collected at the Royal Marsden Hospital in London (UK) as part of an expanded access program (provided free of charge, upon individual unsolicited request by treating clinicians, by Deciphera Pharmaceuticals prior to European Medicines Agency [EMA] / Medicines & Healthcare products Regulatory Agency [MHRA] approval) have been published and included in this submission to support the INVICTUS RCT and demonstrate the generalisability of the results to clinical practice in the UK.⁶⁹ Deciphera Pharmaceuticals was not involved in the data collection and analysis for this study. Data from the Royal Marsden was not included in the economic model due to its retrospective nature, shorter follow-up period and smaller sample size compared with INVICTUS.

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In addition to published data, three advisory boards with oncologists based in the UK were conducted in August 2022, July 2024 and April 2025. All participants had extensive experience in the treatment of advanced GIST and were familiar with the INVICTUS trial and, in the case of the July 2024 and April 2025 meetings, the Royal Marsden expanded access program as well. Insights were used to provide additional evidence relevant to UK clinical practice and to validate the assumptions made in the cost-effectiveness model, and are used throughout the document.^{18,38,70}

2.3 Summary of methodology of the relevant clinical effectiveness evidence

2.3.1 INVICTUS methodology

Trial design

INVICTUS was an international, multicentre, randomised, double-blind, placebo-controlled phase 3 trial in 129 patients who had received 3 or more prior anticancer therapies for advanced GIST. It compared the efficacy of ripretinib plus BSC (hereafter referred to as the 'ripretinib' group) and placebo plus BSC (hereafter referred to as the 'placebo' group) in patients who had received prior treatment with at least imatinib, sunitinib, and regorafenib.¹⁵ The study was conducted at 29 specialised hospitals across 12 countries in North America, Europe, and Asia, including two in the UK.¹⁵

Patients were randomised 2:1 to receive ripretinib 150 mg once daily (QD) or placebo orally in 28-day cycles until disease progression or unacceptable toxicity. Randomisation was stratified by:¹⁵

- Patients who had received 3 vs 4 or more prior anticancer treatments
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 vs 1 or 2

As a part of BSC, permitted concomitant medication included medications for symptomatic relief such as analgesics, laxatives, and antiemetics (Table 5). Medications that increased gastric pH, with the exception of proton pump inhibitors,

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must not have been taken within 2 hours of study drug administration.¹⁹ Surgery or palliative radiotherapy during study treatment was permitted by agreement with the sponsor and investigator if it was in the best interests of the patient.^{19,71}

Table 5: Concomitant medications in the INVICTUS safety population (>40% patients)

Permitted medications (>40%)	Placebo (n=43)* (%)	Ripretinib 150 mg QD (n=85) (%)	Total (n=128) (%)
Analgesics	37 (86.0)	66 (77.6)	103 (80.5)
Antibacterials for systemic use	22 (51.2)	38 (44.7)	60 (46.9)
Drugs for acid related disorders	22 (51.2)	40 (47.1)	62 (48.4)
Drugs for constipation	19 (44.2)	41 (48.2)	60 (46.9)
In addition, the following medications were used in >30% of patients: Antiemetics and antinauseants; diuretics; drugs for functional gastrointestinal disorders; mineral supplements; psycholeptics			

*44 patients were randomised to placebo; one did not receive treatment.

QD: once daily

Source: Deciphera Pharmaceuticals. 2019.¹⁹

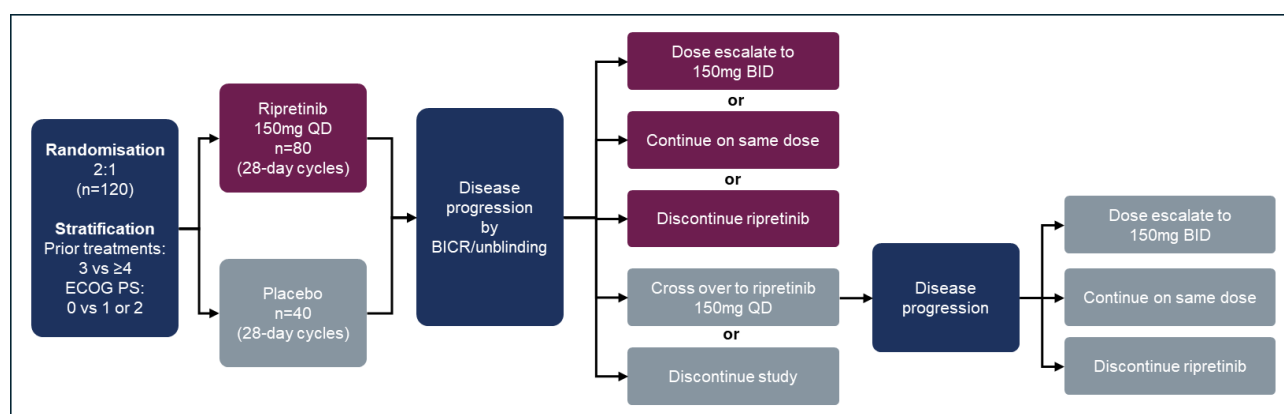
Patients, investigators, and research staff were unblinded to the study drug assignment upon disease progression, as determined by blinded, independent, central review (BICR). Upon disease progression by mRECIST, based on independent radiologic review (IRR), patients randomised to ripretinib 150 mg QD were given the option to continue at an increased dose (150 mg twice a day [BID]), to continue their current dose at 150 mg QD, or to discontinue treatment with ripretinib.¹⁵ Patients randomised to placebo were able to crossover to ripretinib 150 mg QD upon disease progression or discontinue the study, also by mRECIST based on IRR. Patients who crossed over to ripretinib and then experienced a second disease progression were given the option to continue at an increased dose (150 mg BID), to continue their current dose at 150 mg QD, or to discontinue treatment with ripretinib (Figure 2).¹⁵ The option to dose escalate was included to give patients another therapeutic option after disease progression given the limited options at this point in the treatment pathway.

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Nevertheless, across the intent-to-treat (ITT) population approximately three-quarters (75.9%) of ripretinib exposure time was on QD.¹⁵

Patients had a follow-up safety visit 30 days after their final dose and were followed up every 3 months thereafter to collect long-term survival data.¹⁵ Furthermore, ripretinib may have been interrupted or the dose reduced at the discretion of the investigators at any time due to AEs.

Figure 2: INVICTUS study design and treatment allocation



Abbreviations: BID – Twice a day; BICR – Blinded independent central review; ECOG PS – Eastern Cooperative Oncology Group Performance Status; QD – Once a day.

Note: Randomisation was stratified based on prior lines of therapy (3 vs ≥4) and ECOG (0 vs 1 or 2).

Source: Blay et al. 2020,¹⁵ Supplementary Appendix, Figure S1.

For the primary analysis, all efficacy and safety endpoints comparing ripretinib with placebo are based on the double-blind period with a primary completion cut-off date of 31 May 2019.¹⁵ The primary analysis reflects a median follow-up of 6.3 months (interquartile range [IQR] 3.2–8.2) in the ripretinib group and 1.6 months (1.1–2.7) in the placebo group. OS was analysed for the full on-study period, including both the double-blind and open-label periods with a data cut-off on 31 May 2019 for the primary analysis (double-blind) and 15 January 2021 after an additional 19 months follow up (open-label period).²³ This is in addition to an additional data cut in August of 2020.

Eligibility

Patients enrolled in INVICTUS were aged 18 years and older who had a histologically confirmed diagnosis of GIST, at least 1 measurable lesion based on the modified Response Evaluation Criteria in Solid Tumours (mRECIST) version 1.1 criteria, an

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ECOG performance status of 0 to 2, and had progressed on at least imatinib, sunitinib, and regorafenib, or were intolerant to these therapies despite dose modifications. Patients were excluded if they had received an anticancer therapy within 14 days of the study. Key inclusion and exclusion criteria are presented in Table 6.¹⁵

Table 6: Key inclusion and exclusion criteria of INVICTUS

Inclusion criteria	Exclusion criteria
• Aged ≥18 years • Histologic diagnosis of GIST • Patients must have progressed on imatinib, sunitinib, and regorafenib or have documented intolerance to any of these treatments • ECOG PS of 0 to 2 at screening • At least 1 measurable lesion according to the mRECIST v1.1 criteria^a within 21 days of the first dose of study drug • Adequate organ function and bone marrow reserve • Resolution of all toxicities from prior therapy to ≤ Grade 1 (or baseline) within 1 week prior to the first dose of study drug	• Treatment with anticancer therapy, including investigational therapy or investigational procedures, within 14 days or 5x the half-life (whichever was longer) prior to the first dose of study drug. For prior biological therapies, e.g., monoclonal antibodies with a half-life longer than 3 days, the interval was at least 28 days prior to the first dose of study drug. • Prior treatment with ripretinib

^aNon-nodal lesions must be ≥1.0 cm in the long axis or ≥double the slide thickness in the long axis; ^bexcluding alopecia and ≤ Grade 3 clinically asymptomatic lipase, amylase, and creatine phosphokinase (CPK) laboratory abnormalities. Abbreviations: GIST – Gastrointestinal stromal tumour; ECOG PS – Eastern Cooperative Oncology Group Performance Status; mRECIST v1.1 – modified Response Evaluation Criteria in Solid Tumours version 1.1. Source: Blay et al. 2020.¹⁵

Primary and secondary endpoints

The primary efficacy endpoint in the study was PFS, defined as the date from randomisation to the date of progressive disease (PD) or death due to any cause, as assessed by radiologic BICR using the mRECIST version 1.1 criteria.¹⁵ Additionally, during some analysis PFS was subdivided into PFS1, defined as the time from randomisation until PD, and PFS2, defined as the time from the first dose of ripretinib 150 mg BID to PD or death.

The key secondary efficacy endpoint was ORR, defined as a confirmed complete response (CR) or partial response (PR), as assessed by BICR and during the initial assigned study treatment.¹⁵ Other secondary endpoints were OS, time to progression (TTP), time to best response, and duration of response (DOR). HRQoL was assessed

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using the EuroQol 5 dimensions 5 levels (EQ-5D-5L), EuroQol visual analogue scale (EQ-VAS), and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-item (EORTC QLQ-C30) - physical and role functioning domains only.¹⁵ These were all pre-specified analyses in the Statistical Analysis Plan (SAP).

Analysis of time to treatment discontinuation (TTD) was undertaken post-hoc to provide data on continued treatment with ripretinib post-progression required for the cost-effectiveness model.⁷²

Safety assessments included clinical laboratory tests, ECOG performance status, vital signs, weight, 12-lead electrocardiogram (ECG) measurements, left ventricular ejection fraction, physical examinations, and dose reductions, interruptions, or treatment discontinuations.¹⁵

2.3.2 Summary of INVICTUS methodology

The methodology of INVICTUS is summarised in Table 7.

Table 7: Summary of the INVICTUS methodology

INVICTUS (NCT03353753)	
Location	Multinational
Trial design	Phase 3, double-blind, randomised, placebo-controlled, trial
Key eligibility criteria for participants	• Aged ≥18 years • Histologic diagnosis of GIST • Patients must have progressed on imatinib, sunitinib, and regorafenib or have documented intolerance to any of these treatments • ECOG PS of 0 to 2 at screening
Settings and locations where the data were collected	29 specialised hospitals in North America, Europe, and Asia (two in the UK)
Trial drugs	• Ripretinib 150mg QD + BSC (n=85) • Matching placebo 150 mg QD + BSC (n=44) Patients were randomised 2:1 to receive ripretinib or placebo orally in 28-day cycles until disease progression or unacceptable toxicity.
Primary outcome (including scoring methods and	PFS, as assessed by BICR. Tumour assessments were conducted at screening and then every cycle through Cycle

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INVICTUS (NCT03353753)	
timings of assessments)	4. After Cycle 4 (or if the patient was on ripretinib after unblinding), assessments were conducted every other cycle.
Other outcomes used in the economic model/specified in the scope	ORR, OS, AEs, TTD and HRQoL
Pre-planned subgroups	Subgroup analyses of the primary endpoint of PFS were pre-specified. The following subgroup analyses were performed: • Age (18 to 64 vs 65 to 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 PS (0 vs 1 or 2) • Number of prior therapies (3 vs ≥4)

Abbreviations: AE – Adverse event; BICR – Blinded independent central review; BSC – Best supportive care; ECOG PS – Eastern Cooperative Oncology Group Performance Status; GIST – Gastrointestinal stromal tumour; HRQoL – Health-related quality-of-life; OS – Overall survival; PFS – Progression-free survival; QD – Once a day. Source: Blay et al. 2020.¹⁵

2.3.3 Patient baseline characteristics: INVICTUS

Patient characteristics were generally well-balanced across the two treatment groups. There was a similar proportion of males (55% vs 59%), patients in the ECOG performance status strata of 1 or 2 (56% vs 61%) and patients with three prior lines of therapy (64% vs 61%) between the ripretinib and placebo groups, respectively. In both groups, over half of patients were outside the US (53% vs 55%) and the median age was 59 and 65 years, respectively (Table 8).¹⁵

The ripretinib group had a lower proportion of patients aged ≥75 years than the placebo group (9% vs 23%) and a slightly higher frequency of primary gastric tumours (47% vs 41%).¹⁵ A lower frequency of KIT exon 11 mutations was seen in the ripretinib group (55% vs 64%) and PDGFRA mutations were present in 4% in the ripretinib group and none in the placebo group.¹⁵

Subsequent subgroup analyses have shown that these slight imbalances in patient baseline and disease characteristics across the arms of INVICTUS are unlikely to significantly impact the overall treatment effect of ripretinib.¹⁵

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Table 8: Patient baseline characteristics in INVICTUS - double-blind period (ITT population)

	Ripretinib group (n=85)	Placebo group (n=44)
Median age, range (years)	59 (29–82)	65 (33–83)
18–64	57 (67%)	22 (50%)
65–74	20 (24%)	12 (27%)
≥75	8 (9%)	10 (23%)
Sex		
Male	47 (55%)	26 (59%)
Female	38 (45%)	18 (41%)
Race		
White	64 (75%)	33 (75%)
Non-white	13 (15%)	7 (16%)
Not reported	8 (9%)	4 (9%)
Region		
USA	40 (47%)	20 (46%)
Non-USA	45 (53%)	24 (55%)
Number of previous therapies		
3	54 (64%)	27 (61%)
4–7	31 (36%)	17 (39%)
ECOG PS		
0	37 (44%)	17 (39%)
1 or 2	48 (56%)	27 (61%)
Primary tumour site		
Gastric	40 (47%)	18 (41%)
Jejunum or ileum	20 (24%)	8 (18%)
Mesenteric or omental	6 (7%)	6 (14%)
Other	7 (8%)	4 (9%)
Duodenum	2 (2%)	8 (18%)
Colon or rectum	9 (11%)	0
Unknown	1 (1%)	0
Sum of longest diameters of target lesions (mm), median (range)*	123 (28–495)	142 (17–412)
Primary mutation (central testing of tumour tissue)		
KIT exon 9	14 (17%)	6 (14%)
KIT exon 11	47 (55%)	28 (64%)
Other KIT	2 (2%)	2 (5%)
PDGFRA	3 (4%)	0

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	Ripretinib group (n=85)	Placebo group (n=44)
KIT and PDGFRA wild-type	7 (8%)	3 (7%)
Not available† or not done‡	12 (14%)	5 (11%)

Abbreviations: ECOG PS – Eastern Cooperative Oncology Group Performance Status; ITT – Intent-to-treat; PDGFRA – Platelet-derived growth factor receptor α .

* Independent assessment.

† Tumour tissue analysed for baseline mutations but analysis failed.

‡ Biopsy completed per protocol but sample not received for analysis.

Source: Blay et al. 2020, table 1.¹⁵

2.3.4 Royal Marsden expanded access study methodology

The Royal Marsden Hospital, London, UK independently published observational data from the ripretinib expanded access program; Deciphera Pharmaceuticals had no involvement in collecting, analysing or publishing of this data.⁶⁹

Study design

The objective of this retrospective observational study was to describe the outcomes and safety of treatment with ripretinib in a cohort of patients treated in a real-world setting, as part of the expanded access program for ripretinib in the UK prior to EMA/MHRA approval. The use of ripretinib in the UK and Europe prior EMA/MHRA approval was through a free-of-charge expanded access program provided by Deciphera Pharmaceuticals on an ‘as needed’ basis, driven by clinicians’ unsolicited requests following Food and Drug Administration (FDA) approval up until EMA/MHRA approval. Patients who already had access through the expanded access program remained on treatment until clinical benefit was no longer observed or until unacceptable toxicity was seen.⁶⁹

A retrospective review of all patients with advanced (unresectable or metastatic) GIST who commenced ripretinib at The Royal Marsden Hospital, London, UK, between January 2020 and October 2021 was performed. Patients without a confirmed histological diagnosis of GIST and patients who did not start ripretinib at the Royal Marsden (because they were too unwell or they started treatment at a different institution) were excluded.⁶⁹

All patients treated had imaging available for retrospective assessment of radiologic response according to mRECIST 1.1 and had at least one measurable lesion.

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Radiological assessments were performed every 10–14 weeks or when clinically indicated. Data cut-off was 15 January 2023.⁶⁹

Details of the Royal Marsden expanded access program analysis are provided in Table 9 and Table 10.

Table 9: Summary of the Royal Marsden expanded access study with ripretinib

Study	Expanded access program use of ripretinib (DCC-2618) for the treatment of patients with advanced GIST (NCT04148092) ⁷³
Study design	Retrospective observational single centre cohort
Population	Patients with unresectable or metastatic GIST and available clinical and radiological data, who had received at least two prior lines of treatment
Intervention(s)	Ripretinib
Comparator(s)	n/a
Reported outcomes	PFS, TTD, ORR, TBP, OS, AEs

Abbreviations: AE – Adverse event; GIST – Gastrointestinal stromal tumour; ORR – Overall response rate, OS – Overall survival; PFS – Progression-free survival; TBP – Treatment beyond progression; TTD - Time to treatment discontinuation.

Source: Lim et al. 2024.⁶⁹

Table 10: The Royal Marsden expanded access study with ripretinib: inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
- Male or female patients, $\geq$ 18 years of age at the time of informed consent - Histologic diagnosis of GIST - Patients must have received prior treatment with at least 2 of the approved drugs for GIST: comprising imatinib, sunitinib, and/or regorafenib - Resolution to Grade 1 or baseline of all serious toxicities from prior therapy before initiating treatment with ripretinib	- Have started ripretinib treatment at a different institution from the Royal Marsden Hospital, London, UK - Eligible to participate in another ongoing clinical study in which the patient may have access to ripretinib - Received treatment with anticancer therapy, including investigational therapy or investigational procedures, within 7 days or $5 \times$ the half-life (whichever is longer) prior to the first dose of ripretinib. For prior biological therapies (e.g., monoclonal antibodies with a half-life longer than 3 days), the interval must be at least 28 days prior to the first dose of ripretinib - Received prior treatment with ripretinib - Known active central nervous system metastases - A concurrent malignancy for which treatment is being received that may interfere with the potential benefits of ripretinib

Abbreviations: GIST – Gastrointestinal stromal tumour.

Source: ClinicalTrials.gov.⁷³

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Study conduct

Baseline patient characteristics that were collected included but were not limited to: age in years at first ripretinib dose; primary mutation status (KIT and PDGFRA); ECOG performance status (PS); and number and type of previous lines of treatment.

During treatment with ripretinib, patients received a ripretinib starting dose of 150 mg QD but were given the opportunity to dose escalate to 150 mg ripretinib BID at the time of disease progression determined by their treating physician. Due to the possibility for inpatient dose escalation (IPDE), patients were retrospectively assessed as two groups: those receiving 150 mg ripretinib QD; and those with dose escalation upon tumour progression to 150 mg ripretinib BID.⁶⁹

During treatment with ripretinib, information was collected on radiological response, toxicity (according to Common Terminology Criteria for Adverse Events Version 5.0 [CTCAE v5]), dose reduction, IPDE to 150 mg BID dosing, treatment duration and cause of treatment interruption. When documenting the reason for treatment discontinuation, clinical PD was defined as worsening patient-reported symptoms in the presence of radiological signs of PD that did not reach the level required for confirming mRECIST PD. The radiological signs required to reach mRECIST PD include a progressively growing tumour nodule within a pre-existing tumour mass where the lesion was at least 2 cm in size or the lesion had to be expanding on at least 2 sequential imaging studies.^{69,71}

Given the observational nature, the analysis had no predefined sample size and all patients meeting the inclusion criteria were analysed.⁶⁹

Outcomes

Retrospective mRECIST measurements were used to assess PFS, best ORR and time to best response.

Due to the possibility of IPDE, specific PFS endpoints were defined:

- PFS QD was defined as the time from the date of the first 150 mg ripretinib QD dose to the time of mRECIST progression while on this dose or death,

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whichever occurred first.⁶⁹ This endpoint is equivalent to PFS (the primary endpoint) in INVICTUS.

- **PFS BID** was defined in the subgroup of patients undergoing IPDE, as the time from date of the first 150 mg ripretinib BID dose to the time of mRECIST progression while on this dose or death, whichever occurred first.⁶⁹ This endpoint is equivalent to PFS2 in INVICTUS.
- **PFS ITT** was defined as the time from the first 150 mg ripretinib QD dose to: the time of mRECIST progression at this dose for patients who did not undergo IPDE; the time of mRECIST progression at the 150 mg BID dose for patients who did undergo IPDE; or time of death, whichever occurred first.⁶⁹ This endpoint was defined to capture the overall duration of ripretinib treatment regardless of dosage. There was no equivalent endpoint in INVICTUS.

TTD endpoints were defined for the same groups as PFS endpoints. TTD was the time from the first day of ripretinib treatment (at a specified dose) to the last day of ripretinib treatment (at a specified dose) regardless of the cause of treatment discontinuation.⁶⁹

TBP assessed ripretinib treatment beyond disease progression and was defined as the time patients remained on ripretinib between the PFS event and the TTD event dates if the TTD event date was more than 28 days after the PFS event date.⁶⁹

OS was defined as the time from the date of the first 150 mg ripretinib QD dose to the time of death from any cause.⁶⁹

Patient baseline characteristics

In total, 61 patients were registered for the ripretinib expanded access program at the Royal Marsden Hospital. Of these, 16 patients were excluded (1 patient did not have GIST; 4 patients decided not to start ripretinib treatment; 8 patients were too unwell to start ripretinib and 3 patients started ripretinib at a different institution).⁶⁹ As such, 45 patients with available clinical and radiological data were included in the study.⁶⁹

Baseline patient characteristics are reported in Table 11. Information on primary mutational status was not available for 6 patients, and the small bowel was the most common primary tumour site (51.1%). All patients except 1 had metastatic disease
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and an ECOG PS of 1 or 2 whilst 26 (57.8%) patients had received 3 or more prior lines of treatment. All patients had progressed after imatinib and 95.6% of patients had also progressed after sunitinib.⁶⁹

Table 11: Patient baseline characteristics in the expanded access cohort, Royal Marsden, UK

Total Number of Patients	45	100%
Sex		
Female	19	42.2%
Male	26	57.8%
Age		
Median, Q1–Q3	62	57–72
Primary mutational status		
KIT exon 11	33	73.3%
KIT exon 9	3	6.7%
PDGFRA	3	6.7%
N/A	6	13.3%
Primary tumour site		
Stomach	13	28.9%
Small bowel	23	51.1%
Other	9	20.0%
Stage		
Locally advanced	1	2.2%
Metastatic	44	97.8%
1 site	15	34.1%
2 sites	18	40.9%
3 or more sites	11	25.0%
ECOG PS		
0	1	2.2%
1	42	93.3%
2	2	4.4%
Number of previous lines		
2	19	42.2%
3 or more	26	57.8%
Previous lines		
Imatinib	45	100%
Sunitinib	43	95.6%
Regorafenib	24	53.3%
Avapritinib	13	28.9%

Abbreviations: ECOG PS – Eastern Cooperative Oncology Group Performance Status

Source: Lim et al. 2024.⁶⁹

Patients who had only received two prior lines of treatment were also enrolled to provide them with an additional treatment option not otherwise available in the UK.⁶⁹

This was despite regorafenib being reimbursed and available, as clinicians feared the Company evidence submission template for ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments (review of TA881) [ID6496]

expanded access program would have been closed by the time patients were in later lines of therapy.¹⁸ Clinicians in a UK advisory board explained that when patients were given the option of ripretinib or regorafenib, they often chose ripretinib.¹⁸

2.3.5 Expert elicitation or expert opinion

Advisory boards with oncologists based in the UK were conducted in August 2022, July 2024 and April 2025.^{18,38,70} The aim of the advisory boards was to elicit expert insights on:

- the unmet need in advanced GIST in the UK;
- the generalisability of INVICTUS to UK clinical practice, supported by observations from Royal Marsden;
- the assumptions used in the health economic model, including the OS extrapolation and utility values;
- the clinical management of advanced GIST in the UK.

Medical oncologists specialising in the management of advanced GIST in the UK were identified either through their work in specialist sarcoma units/services, their contribution to GIST treatment guidelines and/or their participation as an investigator in GIST clinical trials.

The advisory board held in 2022 included 4 specialists in GIST.⁷⁰ The 2024 advisory board included 7 specialists in GIST, 6 based in the UK and one based in Scotland. A health economist was also present at the advisory board to moderate selected discussions on the cost-effectiveness model.¹⁸ The 2025 advisory board included 3 specialists in GIST all based in the UK.³⁸ All participants across the advisory boards had extensive experience in the treatment of advanced GIST and were familiar with INVICTUS and the Royal Marsden study.

The materials for the three advisory boards included data from INVICTUS, the Royal Marsden expanded access cohort study (2024 and 2025 only) and analyses from the economic model to facilitate the discussion.

Insights from the clinicians are included throughout the dossier. The full reports, which are qualitative in nature and include a summary of the advisory board discussion, are provided as a 'Data on File' references.^{18,38,70}

2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

2.4.1 INVICTUS

Statistical analysis

Primary efficacy analyses were based on the ITT population, defined as all randomised patients (n=129).¹⁵ The safety population was used for safety analyses and included all patients who received at least one dose of study drug (n=128).¹⁵

A sample size of 120 patients (ripretinib, n=80; placebo, n=40) was calculated to provide both power for efficacy and size for the safety database with an assumed 15% patient dropout.¹⁵ Analysis for PFS was stratified by the same factors used for randomisation (3 vs ≥ 4 prior lines of therapy and ECOG performance status 0 vs 1 or 2).¹⁵ The p-value was from a 2-sided stratified log-rank test at 0.05 significance level in testing the hypothesis of no difference between ripretinib and placebo to provide over 90% power to detect a difference in PFS between ripretinib and placebo.¹⁵ This power assumed a median PFS of 4.5 months for ripretinib and 1.0 month for placebo and approximately 80% power to detect a 20% difference in objective response, assuming an ORR of 22% and 2% for ripretinib and placebo, respectively.¹⁵

A Cox regression model was used to obtain the point estimate of the hazard ratio with treatment and randomisation stratification factors as fixed factors and its 95% CI was obtained using Wald method. PFS time was summarised using the Kaplan-Meier methodology, with associated 2-sided 95% CIs. The proportional hazards assumption was examined by visual inspection of the log (-log) plot.¹⁵ The same methodology was used for other time-to-event endpoints (PFS, OS, TTP, and time to best response).

To control for family-wise type I error, a statistical hierarchical testing procedure was used. The hypothesis tests to evaluate the difference between the two treatment

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groups were done at a 2-sided 0.05 level of significance sequentially in the following order:¹⁵

1. The primary endpoint - PFS
2. The key secondary endpoint - ORR
3. OS
4. HRQoL for change from baseline to Cycle 2 on Day 1 in the physical and role functioning domains of the EORTC QLQ-C30 (each at 0.025 level of significance)

If a hypothesis test was found to be non-significant at the $\alpha=0.05$ level, subsequent analyses in the hierarchy were reported as descriptive statistics¹⁵. Other endpoints (e.g. TTP, time to best response) were not included in the hierarchy due to insufficient power.¹⁵

ORR was analysed by an unstratified two-sided 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.

Descriptive statistics were used to summarise safety data and HRQoL variables.¹⁵ HRQoL outcome assessments that were pre-specified in the SAP compared the change from baseline to Cycle 2 Day 1 in scores on the EQ-5D-5L, EQ-VAS and the EORTC QLQ-C30 questionnaires.¹⁶ A t-test was conducted to evaluate changes between groups in EQ-VAS scores from baseline to Cycle 2 Day 1. Analysis of covariance models (ANCOVA) were used to assess change from baseline to Cycle 2 Day 1 in role and physical function domain scores between groups on the EORTC QLQ-C30.¹⁵ EQ-5D-5L was summarised overall by number and percentage for each level of each dimension. For the EQ-5D-5L index (utility) score, an ANCOVA model was used to assess change from baseline to Cycle 2 Day 1 between groups.¹⁶

The efficacy of ripretinib in patients dose escalating to ripretinib 150 BID in the open-label period following disease progression was an exploratory endpoint of INVICTUS, pre-specified in the SAP.^{66,68} The "post inpatient dose escalation" analysis was conducted on the safety population of patients who were treated with ripretinib 150mg BID in the open-label period. PFS1 in the IPDE population was Company evidence submission template for ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments (review of TA881) [ID6496]

defined as the time from randomisation to disease progression. PFS2 was defined as time from the first dose of ripretinib 150 mg BID to disease progression or death. Both PFS1 and PFS2 were assessed by BICR and analysed using Kaplan-Meier methodology.⁶⁶ The same statistical analysis methods used for the ITT population were applied to analyses of the open-label period.⁷¹

A post hoc analysis of OS was conducted for the subgroup of patients in the placebo group who crossed over to ripretinib in the open-label period on disease progression (n=29). The survival curves and median OS of the subgroups are based on the Kaplan-Meier method.¹⁵

A post hoc analysis of TTD was conducted for patients who were randomised to the ripretinib arm. Time was based on a 4-week or 28-day cycle. The analysis considered ripretinib (any dose) discontinuation during the double-blind and open-label periods. The TTD curves and median TTD are based on the Kaplan-Meier method.⁷²

Handling of missing data

Patients who had first disease progression or died after two or more consecutive missed/non-evaluable assessments were censored for the primary PFS endpoint at the time of radiologic assessment immediately prior to the two or more consecutive missed/non-evaluable radiologic assessments.¹⁹ For the secondary endpoint of ORR, patients with an unknown or missing response were categorised as non-responders and were included in the denominator when calculating the proportion.^{15,19,71}

Subgroup analyses

Subgroup analyses of the primary endpoint of PFS were pre-specified.¹⁵ In each subgroup, the hazard ratio (HR) was from Cox regression with treatment as a fixed factor, and the 95% CI of the HR was based on the Wald method. The following subgroup analyses were performed:¹⁵

- Age (18 to 64 vs 65 to 74 vs 75 years or older)
- Gender (Male vs Female)
- Race (White vs non-White vs not reported)

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- Region (US vs non-US)
- Screening ECOG performance status (0 vs 1 or 2)
- Number of prior therapies (3 vs ≥ 4)

Post hoc subgroup analyses of ORR and OS were also performed on the subgroups stated above using the methodology stated above.

2.4.2 Royal Marsden expanded access program

Statistical analysis

Patient characteristics at baseline were reported as median (IQR) or percentages of the total population for continuous and categorical variables, respectively. Median follow-up time was estimated using the reverse Kaplan–Meier method. Survival curves were constructed using the Kaplan–Meier method, and univariate and multivariate Cox proportional hazard regression models were used to assess the prognostic value of baseline covariates. Variables with univariate p value <0.2 were selected for the multivariate models. HR along with their 95% CI were reported. The validity of the Cox proportional hazard assumption was tested for all multivariable models. All analyses were performed using R software version 4.0.3.⁶⁹

Handling of missing data and patient censorship

Patients not experiencing the event were censored at the date of their last radiological evaluation for PFS endpoints, and to the date of their last clinic appointment for TTD and OS.⁶⁹ Two patients with symptomatic and progressive disease were discharged to the local palliative care team for BSC and were then lost to follow-up. To avoid informative censoring, these patients were considered to have experienced an OS event 2 weeks after their last clinic visit.⁶⁹

2.5 Critical appraisal of the relevant clinical effectiveness evidence

2.5.1 INVICTUS

INVICTUS was a double-blind, parallel-group, randomised, placebo-controlled study, which is the gold-standard study design for interventional clinical trials that minimises the risk of confounding factors and allows direct comparison of the relative efficacy of interventions. The study was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation Guidelines for Good Clinical Practice.¹⁵ Randomisation was carried out appropriately, with patients, assessors, and investigators and site staff all blinded to treatment assignment during the double-blind period. There were no imbalances in drop-outs between groups and primary efficacy analyses were based on the ITT population, where the ITT population was defined as all patients who signed the informed consent and were randomised. Therefore, the trial design of INVICTUS was sufficiently robust to answer the decision problem, in assessing ripretinib versus BSC in adult patients with advanced GIST who have received prior treatment with three or more kinase inhibitors, including imatinib.

The handling of missing data is described in Section 2.4. and please refer to Appendix B for complete details on the quality assessment undertaken in the clinical SLR.

2.5.2 Royal Marsden expanded access program

The Royal Marsden observational data is included in this submission as supporting evidence to demonstrate the generalisability of the results of INVICTUS to UK clinical practice. As a non-randomised and non-controlled retrospective study, there are inherent limitations to the statistical validity of the results. Retrospective studies can suffer from limited or missing data, less rigor in data collection (no pre-study analysis plan or protocol) and recall bias, all of which are distinct disadvantages. However, these limitations have been acknowledged by the sponsors and in the original analysis of the data.

The study reviewed patients from a single institution meaning the populations might not be completely representative of the advanced GIST patient population in the UK. Covariate and multivariate analyses were undertaken to identify any confounding factors and consider these in the interpretation of the results. In particular, the cohort included an unusually high prevalence of small bowel GIST; however, it is unlikely to have had a major impact on the results, as the site of tumour origin was not associated with PFS or OS in multivariate analyses.⁶⁹

2.6 Clinical effectiveness results of the relevant studies

2.6.1 Summary of clinical effectiveness

Ripretinib significantly improved median PFS vs placebo (6.3 months vs 1.0 month), reducing the risk of disease progression or death by 85% (HR 0.15; 95% CI 0.09 to 0.25; $p < 0.0001$) in the INVICTUS phase 3 double-blind RCT.¹⁵

- Ripretinib, when used to treat patients through an expanded access program at the Royal Marsden Hospital in London, resulted in a median PFS of 7.9 months (95% CI 5.6–19.3), similar to that achieved in INVICTUS.⁶⁹

Median OS was 18.2 months in the ripretinib group vs 6.3 months in the placebo group (HR 0.41; 95% CI 0.26 to 0.65) after a median initial follow-up of 6.3 months and an additional 19 months of follow-up.²³

- At primary analysis, ripretinib showed a clinically meaningful improvement over placebo in median OS (15.1 months [95% CI 12.3–15.1] vs 6.6 months [4.1–11.6]; HR 0.36, 95% CI 0.21 to 0.62).¹⁵
- The median OS observed in the Royal Marsden expanded access cohort (14.0 [95% CI 9.9–N/A] months) supports the clinical effectiveness of ripretinib in UK real-world practice.⁶⁹

Ripretinib demonstrated durable, clinically meaningful disease control: 56 patients (66%; 95% CI: 55-76) receiving ripretinib experienced stable disease (SD) at 6 weeks and 40 patients (47%; 95% CI 36-58) at 12 weeks, vs 9 patients (20%; 95% CI 10-35) and 2 patients (5%; 95% CI 1-16) treated with placebo, respectively.¹⁵

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- Additionally, fewer patients treated with ripretinib had progressive disease than patients who received placebo; 19% vs 64%, respectively, at primary analysis.¹⁵
- Ripretinib demonstrated a clinically meaningful benefit to patients, with most patients achieving PR or SD (75%) compared to only 20% in the placebo arm, at primary analysis.
- In patients treated under the Royal Marsden expanded access program, 85.7% had a best response to ripretinib QD of PR or SD, supporting the real-world effectiveness of ripretinib in UK clinical practice.⁶⁹

Ripretinib is well-tolerated and has an acceptable safety profile.

- The majority of treatment-related treatment emergent adverse events in patients receiving ripretinib were grade 1-2, and were alopecia (49%), myalgia (27%), nausea (25%), fatigue (24%), palmar–plantar erythrodysesthesia (21%) and diarrhoea (20%).¹⁵
- Treatment-related serious adverse events were reported in eight (9%) of 85 patients who received ripretinib and three (7%) of 43 patients who received placebo.¹⁵
- Rates of discontinuation (5% vs 2%) and dose reduction (6% vs 2%) due to adverse reactions were low across both the ripretinib and placebo arms, respectively.¹⁵
- The safety profile of ripretinib in the Royal Marsden expanded access program was in line with INVICTUS.⁶⁹

Despite advanced disease, patients treated with ripretinib maintained quality-of-life (QoL) and function over approximately 8 months; the same measures declined sharply for patients on placebo after just 1 month.¹⁶

- Patients having ripretinib reported stable scores on all pre-specified patient-reported outcome (PRO) measures (EQ-5D-5L VAS and EORTC QLQ C30) up to Cycle 10. In contrast, PROs declined sharply in the placebo arm.¹⁶
- Patients receiving ripretinib demonstrated clinically-relevant differences vs placebo in self-reported health (+3.7 vs -8.9; p=0.004), physical function (+1.6 vs -8.9; p=0.004) and role function (+3.5 vs -17.1; p=0.001).¹⁶

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- Patients receiving ripretinib had a longer time until definitive deterioration (TUDD) in all assessed PRO measures compared with placebo.⁵⁶
- The median TUDD for overall health and QoL was not reached at 56 weeks for patients receiving ripretinib vs 7.7 weeks for patients receiving placebo.⁵⁶
- When considering individual INVICTUS patients, the median TUDD in the pre-specified PROs was greater than median PFS, suggesting that patients' use of ripretinib is not limited by toxicity and QoL is maintained during post progression use of ripretinib.⁵⁶

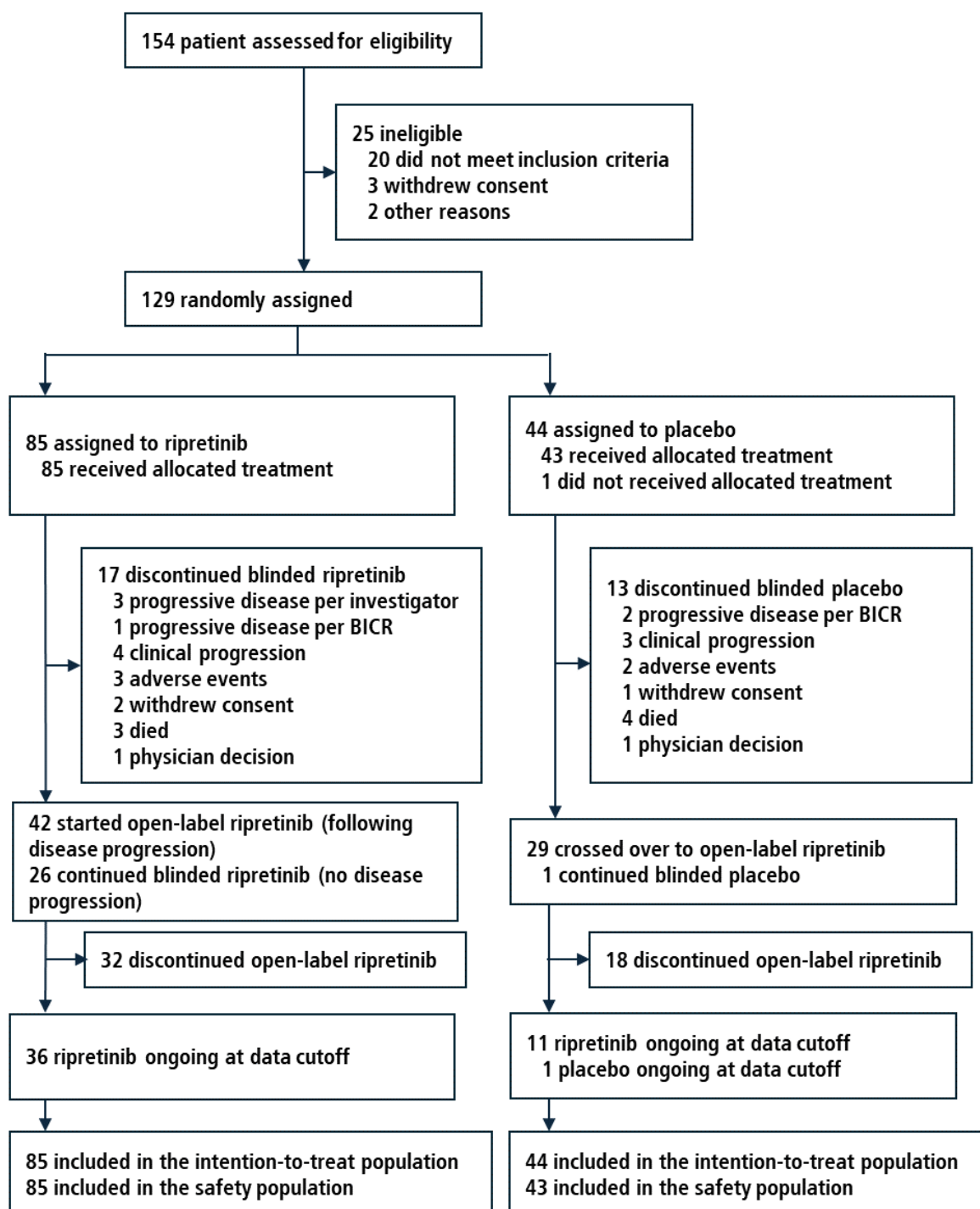
2.6.2 INVICTUS

Patient disposition

A total of 129 patients were enrolled in the trial, of whom 85 were randomised to the ripretinib arm, and 44 were randomised to the placebo arm (Figure 3). Patient withdrawals in the ripretinib and placebo group were equivalent (2.4% vs 2.3%) in the double-blind period (ITT population) and no patient was lost to follow-up. One patient randomised to the placebo group was not treated and not included in the safety population (n=128).¹⁵

Of patients randomised to the placebo group, 29/44 crossed over to open-label ripretinib 150 mg QD after disease progression. At primary analysis, 21.1% (n=27) of patients remained on their blinded treatment in the double-blind period (26 in the ripretinib group and one in the placebo group).¹⁵ Twenty percent of patients in the ripretinib group and 30.2% in the placebo group discontinued treatment in the double-blind period; the most common reasons were clinical progression (ripretinib, n=4; 4.7% vs placebo, n=3; 7.0%) and death (ripretinib, n=3; 3.5% vs placebo, n=4; 9.3%), respectively.¹⁵

Figure 3: Flow of participants in INVICTUS, data cut-off 31 May 2019



Abbreviations: BICR – Blinded independent central review.

Data reported as of the cut-off date for the primary completion date (31 May 2019).

Note: not for reproduction

Source: Blay et al, 2020.¹⁵

The median relative dose intensity in the double-blind period was 100% (IQR 98.1 to 100.0) for the ripretinib group and 97% (86.5 to 100.0) for the placebo group.¹⁵ Treatment compliance was high ($\geq 80\%$) in both groups during the double-blind period (98.8% of patients in the ripretinib arm and 83.7% in the placebo arm).^{15,51} The mean (standard deviation [SD]) treatment duration for the ripretinib arm (24.44 [13.941] weeks) was longer than the treatment duration for the placebo arm (8.25 [6.757] weeks).^{19,51}

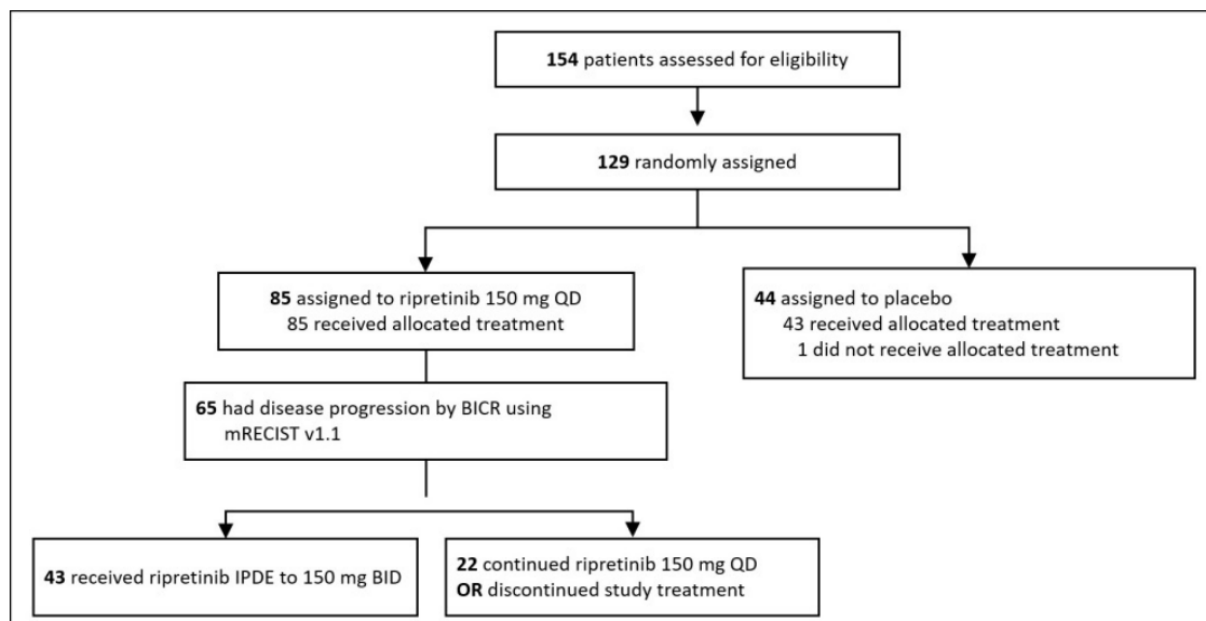
At data cut-off of 10 August 2020, 65 patients in the ripretinib group had progressed, of whom 43 dose-escalated to ripretinib 150 mg BID; 22 patients either continued ripretinib 150 mg QD or discontinued (Figure 4).⁶⁶ Based on the ITT population, 66% of patients randomised to placebo switched to ripretinib after disease progression (n=29 of 44 patients; 1 patient did not receive the allocated treatment, 4 patients died and 10 patients did not switch to ripretinib).^{15,66} Of the 29 patients who crossed over from placebo to ripretinib 150 mg QD, 34% escalated to ripretinib 150 mg BID following a second disease progression (n=10 of 29; 10 continued with ripretinib 150 mg QD and 9 discontinued treatment).

As of January 2021, 63 of the 85 patients originally randomised to ripretinib had entered the open-label period following disease progression based on independent radiological review.⁷⁴ Of those, 19 continued to receive 150 mg QD and 44 underwent IPDE to 150 mg BID. A final total of 30 participants (68%) who received placebo in the double-blind period crossed-over to receive ripretinib 150 mg QD in the open-label period; 16 subsequently dose escalated to 150 mg BID following progression with QD dosing.⁷⁴

Clinicians in a UK advisory board estimated that approximately 80% of patients would be expected to continue ripretinib post-progression in UK clinical practice.³⁸ This aligns with the proportion of patients continuing ripretinib post-progression in INVICTUS. Clinicians also estimated that approximately 50% of those on post-progression ripretinib (i.e., 40% of the total population) would dose escalate if such dosing was routinely commissioned.³⁸ This is lower than that seen in INVICTUS, likely due to patients in routine clinical practice being less fit than those recruited to clinical trials.

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Figure 4: Flow of participants in INVICTUS, data cut-off August 10, 2020



Abbreviations: BICR – Blinded independent central review; BID – twice a day; IPDE - Inpatient dose escalation; mRECIST - Modified response evaluation criteria in solid tumors; QD - Once a day.

Data reported as of August 10, 2020.

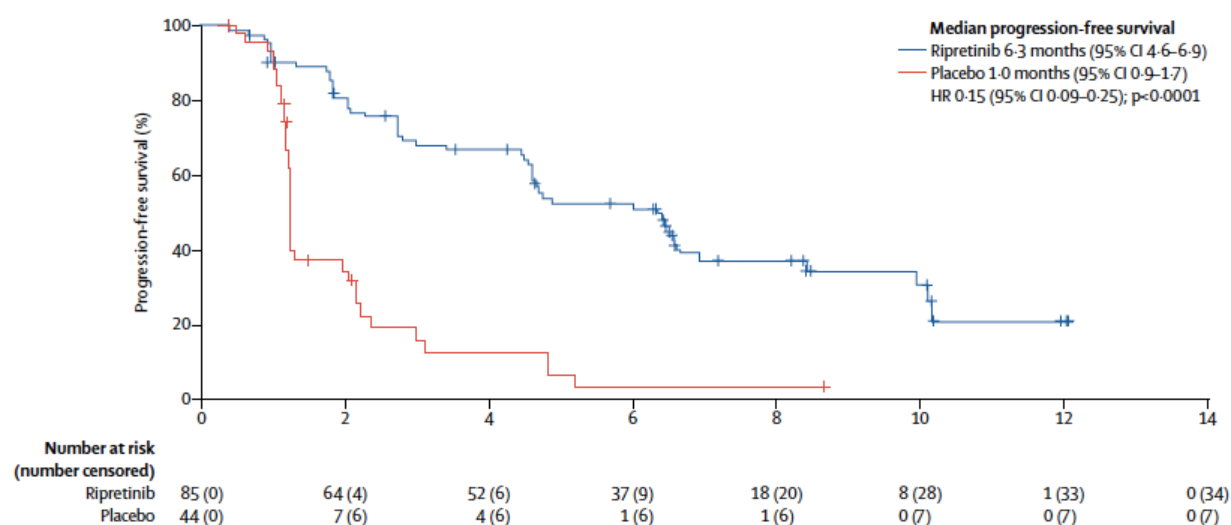
Note: not for reproduction

Source: Zalcberg et al. 2021⁶⁶

PFS – primary endpoint

As of the 31 May 2019 data cut-off, 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.¹⁵ A statistically significant benefit was seen for the primary endpoint, with a median PFS of 6.3 months (95% CI 4.6 to 6.9 months) in the ripretinib group vs 1.0 month (95% CI 0.9 to 1.7 months) in the placebo group, as assessed by BICR.¹⁵ The risk of disease progression or death was significantly reduced by 85% for patients treated with ripretinib compared with placebo (HR 0.15; 95% CI 0.09 to 0.25; $p < 0.0001$).¹⁵ The PFS Kaplan-Meier curve is shown in Figure 5.

Figure 5: Kaplan-Meier PFS curve as assessed by BICR (ITT population, data cut-off 31 May 2019)



Abbreviations: BICR – Blinded independent central review; CI – Confidence interval; HR – Hazard ratio; ITT – Intent-to-treat; PFS – Progression-free survival.

Note: crosses denote censoring of data.

Source: Blay et al. 2020,¹⁵

PFS results for the double-blind analysis period are summarised in Table 12. At 6 months, 51% of patients (95% CI 39.4% to 61.4%) in the ripretinib group were progression-free compared with 3.2% for the placebo group (95% CI 0.2% to 13.8%).¹⁵

Table 12: Summary of PFS results as assessed by BICR (ITT population, data cut-off 31 May 2019)

	Ripretinib (n=85)	Placebo (n=44)
6-month PFS n (%)	43 (51%)	1 (3.2%)
PFS event n (%)	51 (60%)	37 (84%)
Patients censored n (%)	34 (40%)	7 (16%)
Median PFS (95% CI)	6.3 months (4.6 to 6.9)	1.0 month (0.9 to 1.7)
HR (95% CI)*	0.15 (0.09 to 0.25)	
p-value**	p<0.0001	

Abbreviations: BICR – Blinded independent central review; CI – Confidence interval; HR – Hazard ratio; ITT – Intent-to-treat; PFS – Progression-free survival.

* Calculated using Cox regression model, which includes treatment and randomisation stratification factors as fixed factors; 95% CI is based on Wald method.

** p-value is based on 2-sided stratified log-rank test.

Source: Blay et al. 2020,¹⁵

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Disease progression or death (PFS event) occurred in 60% of patients in the ripretinib group (34 patients [40%] were censored) and in 84% in the placebo group (7 patients [16%] were censored).¹⁵

Median PFS estimates from subsequent analyses, using data cut-off dates of 9 March 2020 and 15 January 2021, were similar to those reported for the primary analysis, with a median PFS of 6.3 months (95% CI 4.6 to 8.1 months) in the ripretinib group vs 1.0 month (95% CI 0.9 to 1.7 months) in the placebo group (HR 0.16; 95% CI 0.10 to 0.27) at both time points.^{23,65}

PFS - exploratory analyses

PFS after crossover from placebo to ripretinib

A prespecified exploratory analysis of PFS in the open-label period was conducted for the 29 patients randomised to placebo who crossed over to ripretinib 150 mg QD at their first disease progression (data cut-off 31 May 2019). The time from ripretinib initiation after crossover to second disease progression or death is referred to as PFS2.⁶⁴ Median PFS2 was 4.6 months (95% CI 1.8 months to not estimable). Of the 29 patients, 45% (n=13) had a PFS event and 55% (n=16) were censored. A PFS benefit was seen as early as 1 month after initiating treatment (Figure 6 and Table 13).⁶⁴

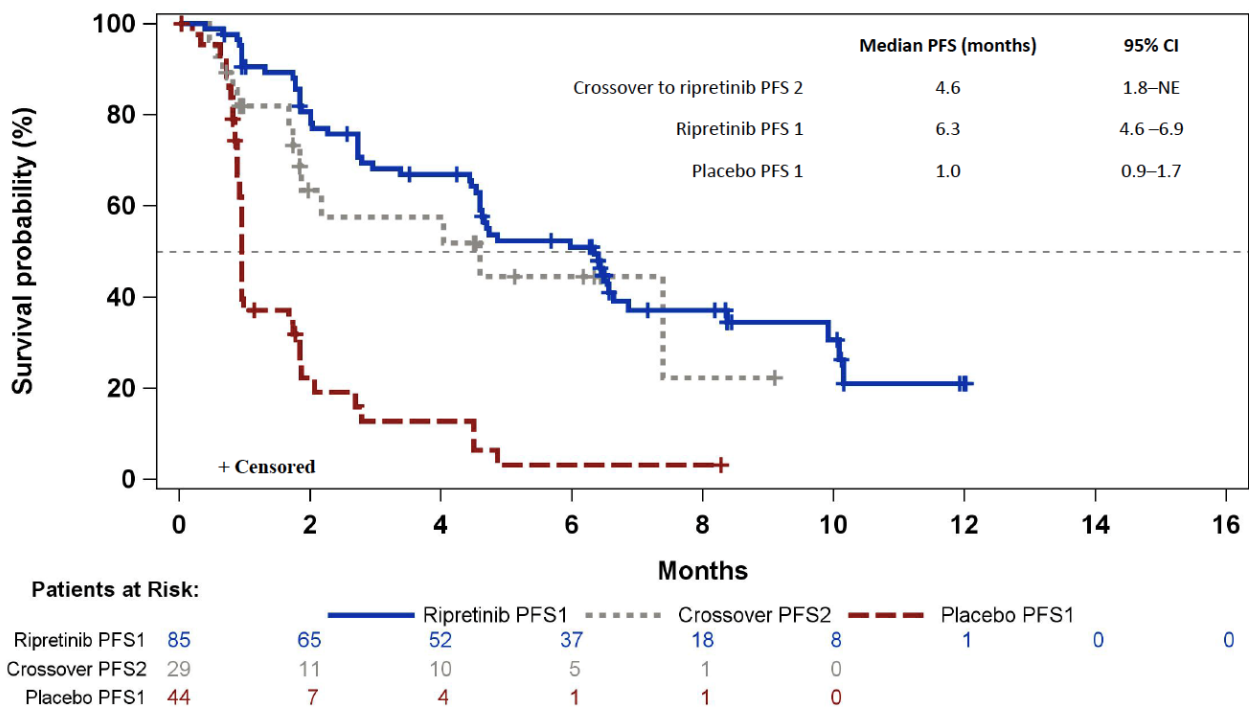
Table 13: Exploratory analysis of PFS following crossover from placebo to ripretinib 150 mg QD compared with PFS outcome in the double-blind period

	Open-label period	Double-blind period	
	Crossover to ripretinib PFS2 (n=29)	Ripretinib PFS1 (n=85)	Placebo PFS1 (n=44)
Patients with a PFS event n (%)	13 (45%)	51 (60%)	37 (84%)
Censored patients n (%)	16 (55%)	34 (40%)	7 (16%)
Median PFS (95% CI)	4.6 (1.8 to NE)	6.3 (4.6 to 6.9)	1.0 (0.9 to 1.7)

Abbreviations: CI - Confidence interval; PFS - Progression-free survival; NE - Not estimable; QD - Once a day. PFS1 indicates PFS during the double-blind period and PFS2 indicates crossover patient's time from ripretinib initiation to progression or death.

Source: Serrano et al. 2020 World Congress on Gastrointestinal Cancer, virtual conference,⁶⁴ slide 9.

Figure 6: Exploratory analysis of PFS during the open-label period in patients (n=29) crossing over to ripretinib 150 mg QD



Abbreviations: CI - Confidence interval; NE – Not estimable; PFS - Progression-free survival; QD - Once a day. PFS1 indicates PFS during the double-blind period and PFS2 indicates a crossover patient's time from ripretinib initiation to progression or death.

Source: Serrano et al. 2020 World Congress on Gastrointestinal Cancer, virtual conference,⁶⁴ slide 9.

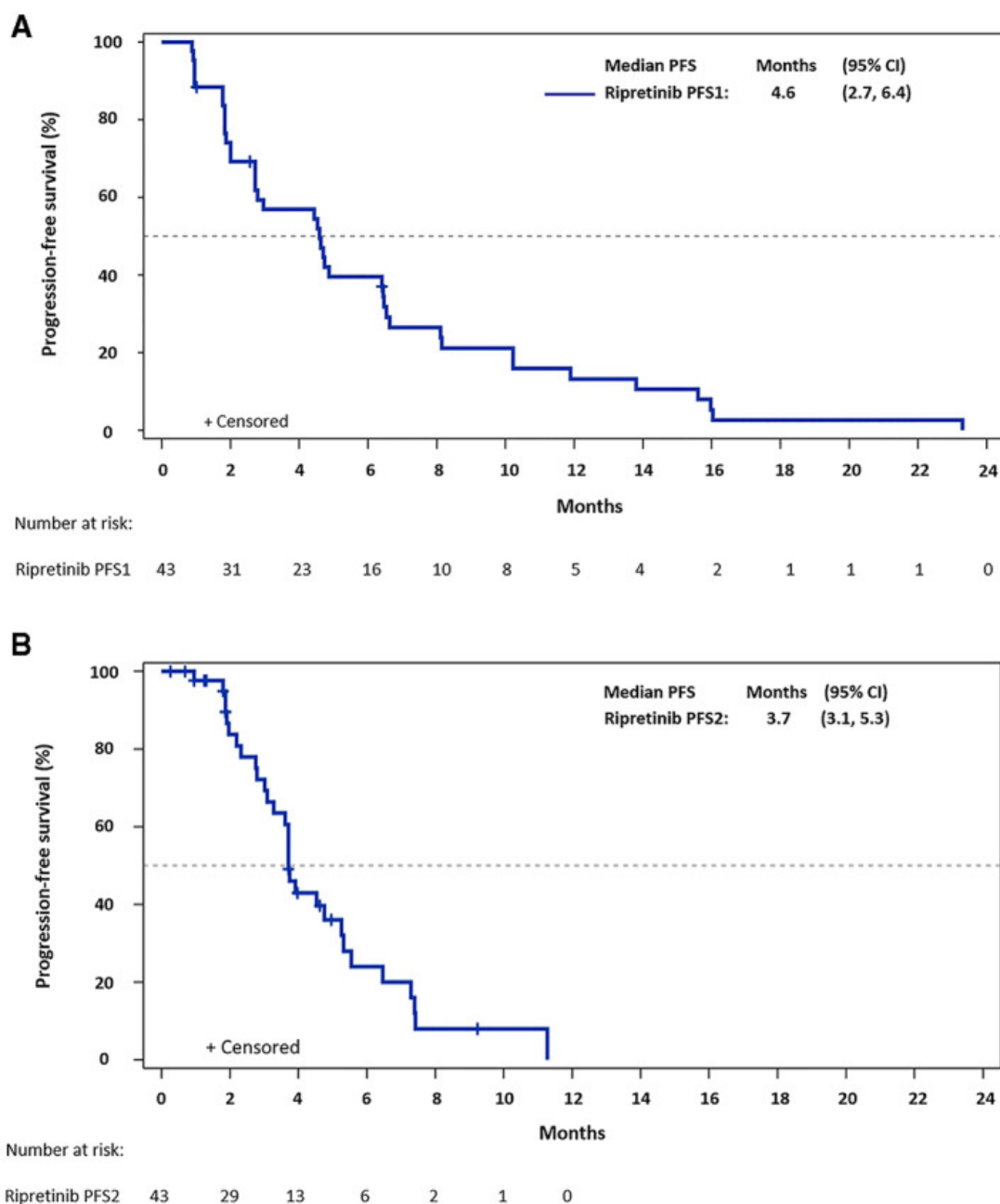
PFS after IPDE to ripretinib 150 mg BID

The occurrence of PFS after IPDE to ripretinib 150 mg BID was a pre-specified exploratory endpoint of INVICTUS.⁶⁶ As of the data cut-off of 10 August 2020, 43 of the 85 patients randomised to ripretinib 150 mg QD had undergone dose escalation to 150 mg BID following disease progression as assessed by BICR.⁶⁶

Median PFS1 in the IPDE group was 4.6 months (95% CI 2.7 to 6.4) and median PFS2 (i.e., post dose escalation) was 3.7 months (95% CI 3.1 to 5.3) (Figure 7). The median PFS2/PFS1 ratio was 80%.⁶⁶

Ripretinib was well-tolerated among IDPE patients at both the 150 mg QD and BID dose periods. The safety profile of ripretinib 150 mg was acceptable during the dose escalation period. The most common grade 3/4 TEAEs occurring in >5% of patients were anaemia (14%) and abdominal pain (7%).⁶⁶

Figure 7: Kaplan-Meier plots of PFS in patients undergoing ripretinib IPDE to 150 mg BID



Abbreviations: BID – Twice a day; CI - Confidence interval; PFS - Progression-free survival.

(A): PFS in the ripretinib 150 mg once daily (QD) period (PFS1). (B): PFS in the ripretinib 150 mg BID period (PFS2). Of the 43 ripretinib IPDE patients, 3 who had progressive disease during ripretinib 150 mg QD were censored due to introduction of a new anticancer therapy or surgery/radiation; 10 were censored during the ripretinib 150 mg BID period for multiple end-of-treatment reasons.

Source: Zalcborg et al. 2021⁶⁶

Overall, these results suggest that ripretinib treatment after radiological progression may provide additional clinical benefit for patients with ≥ 4 L GIST. This aligns with Company evidence submission template for ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments (review of TA881) [ID6496]

clinical practice where patients with advanced GIST may remain on their current line of therapy post progression if it still provides clinical benefit, such as symptom control.¹⁷ Clinical advisory boards have confirmed that the proportion of patients who remained on TBP during INVICTUS reflects anticipated clinical practice in the UK.^{18,38} The analysis only includes patients who dose escalated to 150 mg BID, and the efficacy of continuing ripretinib 150 mg QD after progressive disease could not be assessed given the limited number of patients and multiple reasons for continuing ripretinib 150 mg QD (not reported during the study) after disease progression. A comparison of PFS for patients who dose escalated to 150 mg BID vs those continuing ripretinib 150 mg QD was, therefore, not possible.⁶⁶

OS – secondary endpoint

OS analyses were conducted for the full on-treatment period, including the double-blind and open-label periods. Patients achieved a clinically meaningful survival benefit when treated with ripretinib vs placebo. As of data cut-off on 31 May 2019, 31% of patients in the ripretinib group (69% censored), and 59% in the placebo group (41% censored) had died (Table 14).¹⁵ Median OS was 15.1 months (95% CI 12.3 to 15.1) for the ripretinib group and 6.6 months (4.1 to 11.6) for the placebo group.¹⁵ Ripretinib reduced the risk of death by 64% vs placebo (HR 0.36; 95% CI 0.21 to 0.62).¹⁵ The estimated 12-month OS rate was 65.4% (95% CI 51.6% to 76.1%) for the ripretinib group and 25.9% (95% CI 7.2% to 49.9%) for the placebo group.¹⁵

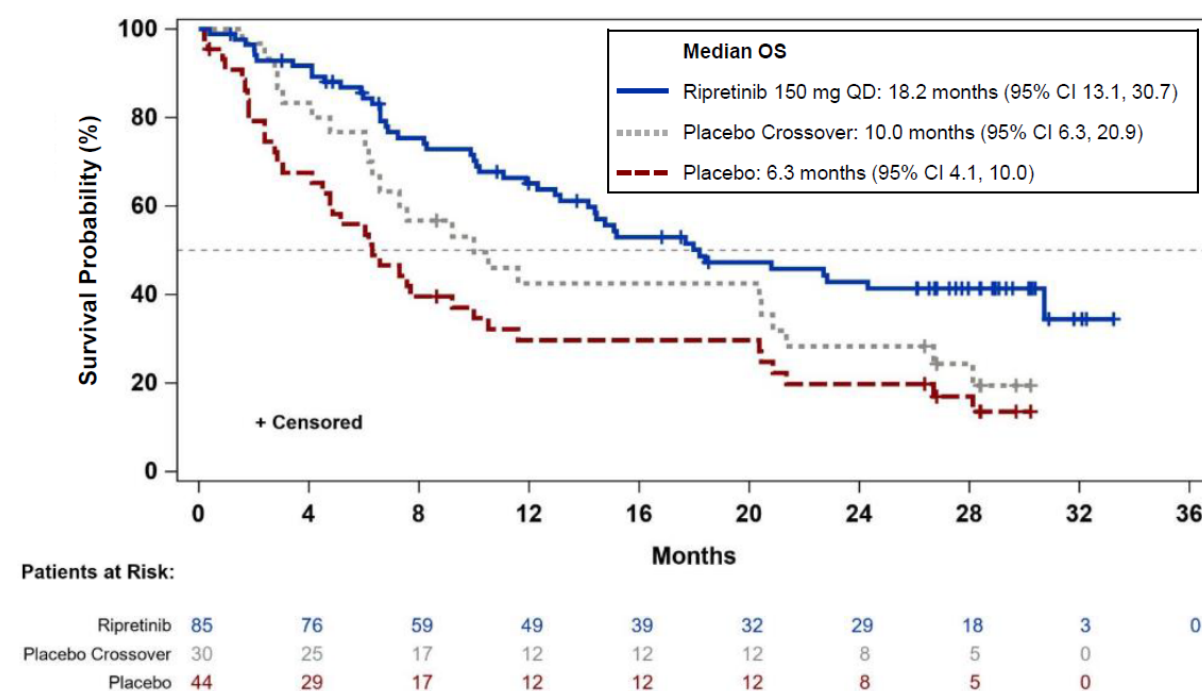
The OS endpoint was not evaluated for statistical significance as a result of the hierarchical testing procedure and the ORR not reaching statistical significance.¹⁵

From analysis of more mature OS data (data cut-off 15 January 2021), estimated median OS was 18.2 months for the ripretinib group (95% CI 13.1 to 30.7 months) (Figure 8). Median OS remained the same for the placebo group (6.3 months; 95% CI 4.1 to 10.0 months; HR 0.41; 95% CI 0.26 to 0.65). At analysis, 54% (n=46/85) of patients in the ripretinib group and 82% (n=36/44) of patients in the placebo group had died.²³ This improvement in median OS seen in longer-term analyses supports the ability of ripretinib to confer a clinically meaningful survival benefit; the continued low

median OS rate observed in the placebo group reflects the aggressive nature of advanced GIST.³⁸

Additionally, patients crossing over from placebo to ripretinib at disease progression (n=29/44) demonstrated a survival benefit (median OS of 11.6 months [95% CI 6.3 to NE]) vs patients who remained on placebo (1.8 months [95% CI 0.9 to 4.9]) (Appendix C).¹⁵ At follow-up analysis (data cut-off January 2021) the median OS for patients who crossed over to ripretinib was 10 months (95% CI 6.3 to 20.9) (Figure 8).²³

Figure 8: Kaplan-Meier OS curves in INVICTUS (ITT population, data cut-off 15 January, 2021)*



Abbreviations: CI - Confidence interval; OS - Overall survival.

* Owing to the hierarchical testing procedures of the endpoints, OS endpoint could not be formally tested because the objective response rate was not statistically significant.

Source: von Mehren et al. 2021²³ Figure 6.

Table 14: Summary of OS results (ITT population)

	Ripretinib (n=85)	Placebo (n=44)
<u>31 May 2019 data cut-off</u>		
12-month OS rate (%)	65%	26%
Patients with an OS event n (%)	26 (31%)	26 (59%)
Patients censored	59 (69%)	18 (41%)
Median OS (95% CI)	15.1 months (12.3 to 15.1)	6.6 months (4.1 to 11.6)
HR (95% CI)*	0.36 (0.21 to 0.62)	
<u>15 January 2021 data cut-off</u>		
24-month OS rate (%)	43%	20%
Patients with an OS event n (%)	46 (54%)	36 (82%)
Patients censored	39 (46%)	8 (18%)
Median OS (95% CI)	18.2 months (13.1 to 30.7)	6.3 months (4.1 to 10.0)
HR (95% CI)*	0.41 (0.26 to 0.65)	

Abbreviations: CI - Confidence interval; HR - Hazard ratio; ITT - Intent-to-treat; OS - Overall survival.

*Calculated using the Cox regression model, which includes treatment and randomisation stratification factors as fixed factors; 95% CI based on Wald method.

Note: OS is defined as the time from the date of randomisation to the date of death or censoring at the date of last follow-up; patient groups are based on the treatment initially assigned. Due to the hierarchical testing procedure, OS was not formally tested for statistical significance as the ORR was not significant; the nominal p-value displayed is based on a 2-sided stratified log-rank test.

Source: Blay et al. 2020,¹⁵ ; von Mehren et al, 2021²³

OS post hoc analyses: OS after IPDE to ripretinib 150 mg BID

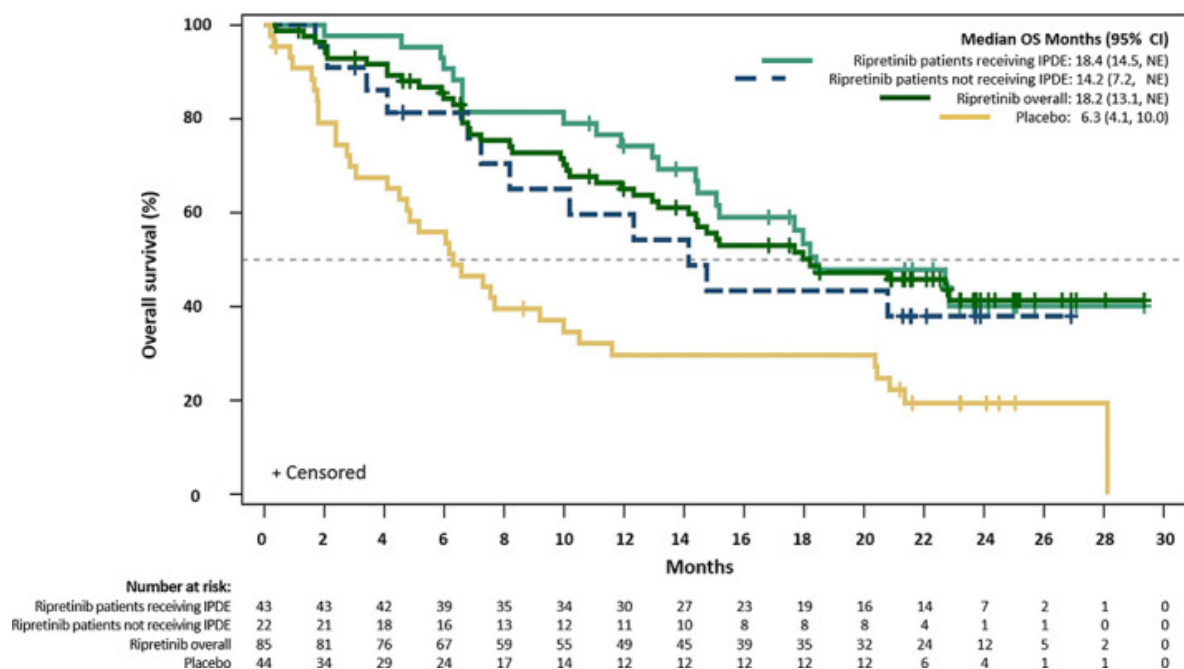
A number of post hoc analyses were considered and UK clinician advisory boards were undertaken to quantify the impact of dose escalation on OS in INVICTUS.

Open-label BID vs QD OS analysis

As of data cut-off of 10 August 2020, 43 of the 85 patients randomised to ripretinib 150 mg QD dose escalated to 150 mg BID following disease progression on by BICR (Figure 9). Of those randomised to ripretinib 150 mg QD with disease progression, 22 did not undergo IPDE but either continued with ripretinib 150 mg QD or discontinued study treatment. The median OS for patients who underwent IPDE was 18.4 months. Company evidence submission template for ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments (review of TA881) [ID6496]

(95% CI, 14.5–NE) vs 14.2 months (95% CI, 7.2–NE) for those who did not (HR, 0.74; 95% CI, 0.37–1.49; Figure 9).⁶⁶

Figure 9: Kaplan-Meier OS estimates in INVICTUS comparing patients who did and did not undergo IPDE (data cut-off 10 August 2020)



Abbreviations: CI - Confidence interval; IPDE – Inpatient dose escalation; NE – Not estimable; OS - Overall survival.

Source: Zalcborg et al. 2021⁶⁶

This post hoc analysis presents a naïve OS comparison of patients randomised to ripretinib 150 mg QD who did and who did not undergo IPDE at disease progression. In addition to the inherent limitations of post hoc analyses (reduced statistical power,

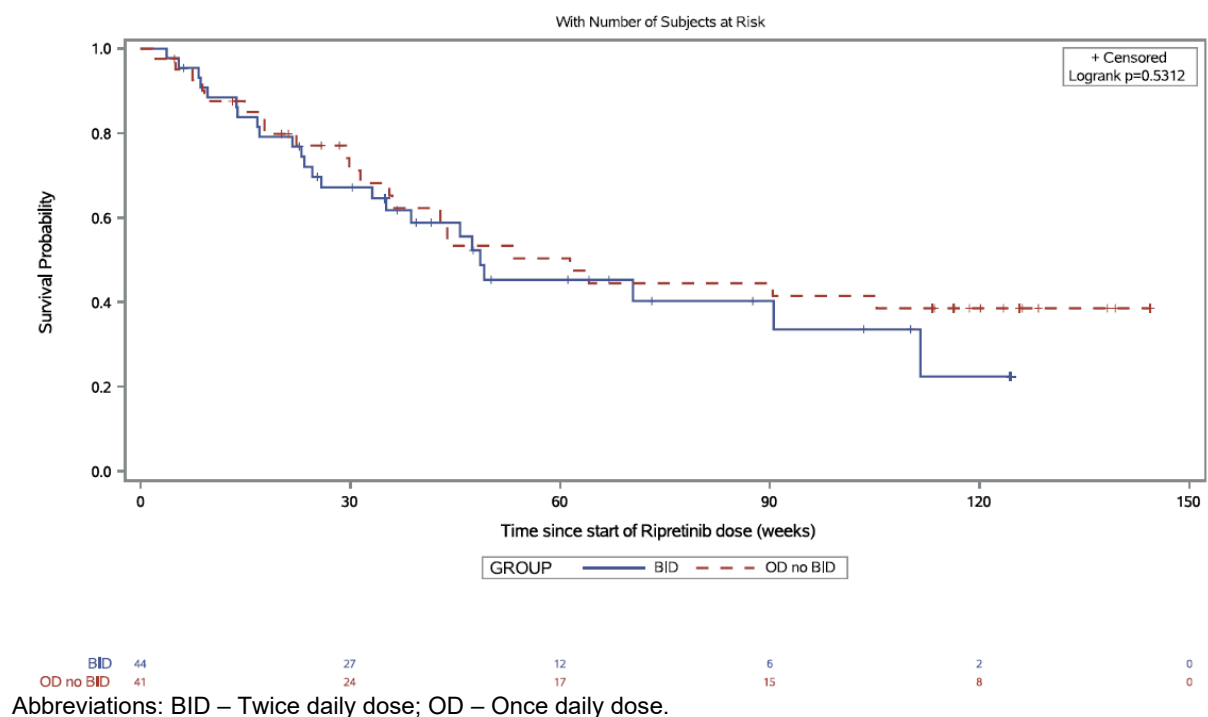
risk of confounding/bias), this analysis was not adjusted for possible predictive or prognostic factors.⁷⁵ In particular, at the time of progressive disease, 51% of patients who dose escalated had an ECOG of 0 whereas 18% who remained on QD dosing had an ECOG of 0.⁶⁶ ECOG has been identified as a prognostic factor, and a lower score is significantly associated with longer survival in patients with advanced GIST.^{46,76,77} A UK advisory board confirmed that ECOG is a key treatment effect modifier for this patient population. Therefore, an imbalance in ECOG status would have contributed to the perceived benefit in the IPDE population vs the population who did not undergo IPDE. Clinicians indicated that patients remaining on QD dosing

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represent a less fit patient population with a poorer prognosis. This analysis was also based on a small number of patients. Taking these factors into account, any conclusions drawn from these analyses are considered highly uncertain.

An alternative naïve analysis suggests that the impact of dose escalation was negligible. For patients who did not dose escalate, Figure 10 plots the survival probability from the start of the trial (first QD dose) to death, and for patients who did dose escalate Figure 10 plots the survival probability from first BID dose to death. This suggests that the chance of survival is similar once a patient starts ripretinib treatment from the initiation of either dose.

Figure 10: Time from the start of ripretinib QD or BID, for patients randomised to ripretinib



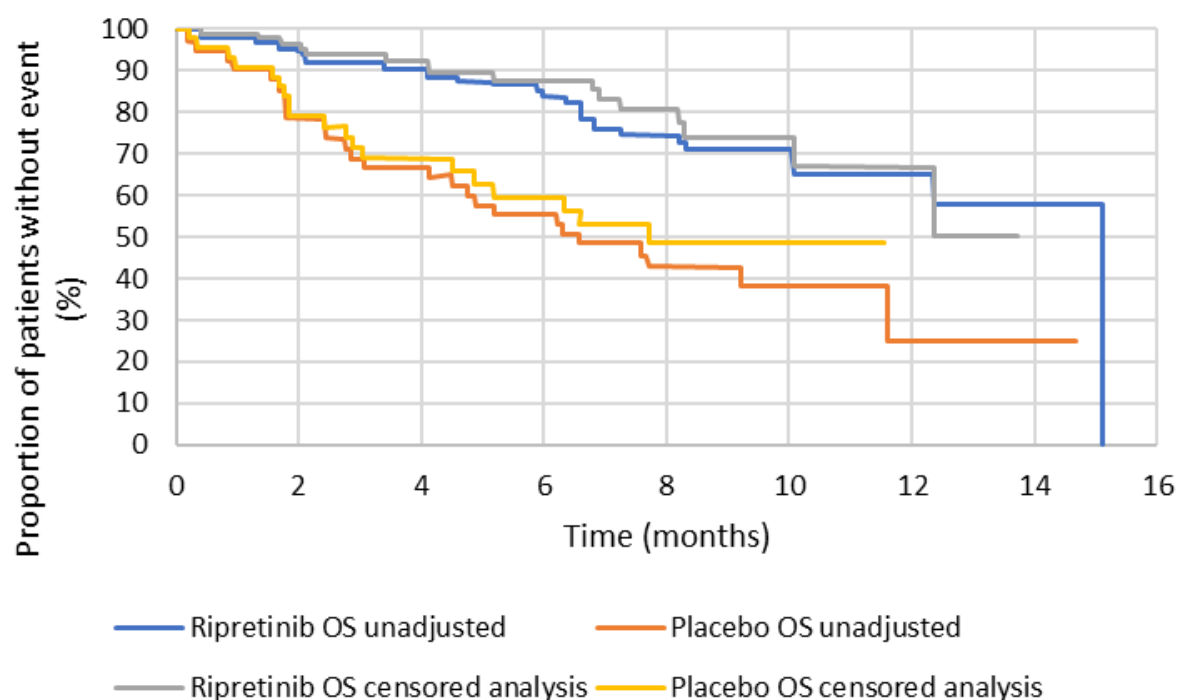
This analysis is subject to some of the limitations as that of Zalcborg et al. However, disease characteristics data collected at the start of treatment (i.e., ripretinib QD for non-escalators, ripretinib BID for escalators) were broadly comparable for the two groups in Figure 10. Of note, although patients who dose escalated started treatment several months later, 51% had an ECOG of 0 at the time of dose escalation vs 44% of patients at trial baseline.⁶⁶

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Censored BID-dosing analyses

To further understand the impact of IPDE on the OS, two other post hoc sensitivity analyses were undertaken. The first analysis censored patients who underwent dose increase to 150 mg BID after progression in the open-label phase of the study. OS was analysed over the full study duration and all patients who dose escalated (whether originally randomised to ripretinib or placebo) were censored in the analysis. This analysis estimated a longer median OS for both groups and an improved OS HR at the primary analysis and subsequent data cut-offs compared with the pre-specified OS analysis (Figure 11).⁷⁸

Figure 11: Post hoc sensitivity analysis of unadjusted OS (ITT population; primary analysis) vs OS with patients who received ripretinib 150 mg BID after disease progression censored



Abbreviations: BID – Twice daily; ITT – Intention-to-treat; OS – Overall survival

Source: Adapted from Gemeinsamer Bundesausschuss (G-BA), Ripretinib (QINLOCK) Submission for Reimbursement, Module 4, 2022,⁷⁸ Blay et al. 2020¹⁵

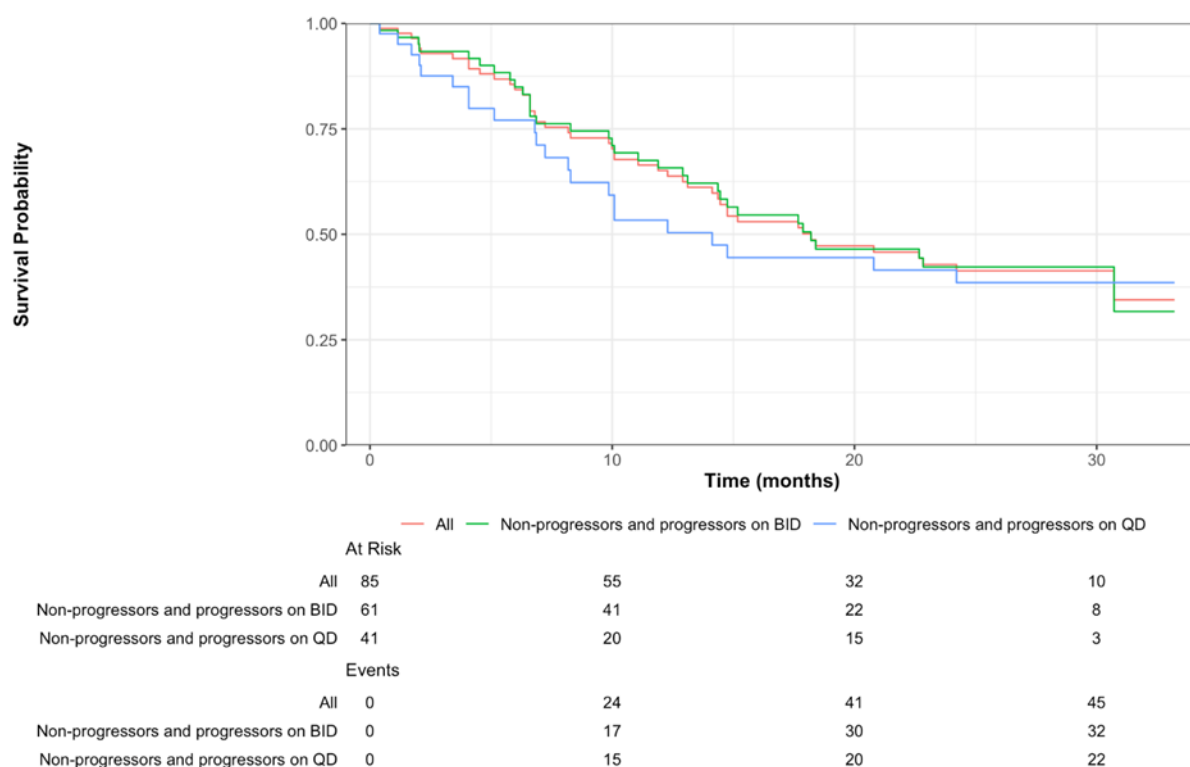
This naïve analysis suggests that the cohort of patients who did not undergo IPDE (i.e., those who: did not experience progression/second progression in the placebo arm and remained on QD dosing; or experienced progression and chose to remain on

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QD dosing) achieved similar, or even slightly longer OS compared with the cohort of patients where approximately a third underwent IPDE. This analysis considers the effect of IPDE on both study arms, thereby presenting a more balanced approach with regards to the OS HR. It also preserves the original data before disease progression, only adjusting for post-progression benefit. However, there is still a risk of bias that is associated with informative censoring and loss of data over time.

To explore this approach further a second, similar, censoring analysis was conducted. This compared the impact on OS of censoring, after disease progression, patients who dose escalated vs patients who remained on QD. This analysis indicates that median OS is lower if patients on BID are censored compared to when patients on QD are censored (Figure 12). However, although there is an early separation of survival curves, they converge by 20 months, suggesting limited difference in long-term survival. This complements the clinician view as they felt that BID dosing is unlikely to shift the shape of the survival curve, stating that patients remaining alive in the longer term, where the survival curves converge, probably have a biologically better disease and would progress slowly, whether on QD or BID dosing.¹⁸

Figure 12: Post hoc sensitivity analysis of unadjusted OS (ITT population; 15 January 2021) vs OS with cohort censoring after disease progression



Abbreviations: BID – Twice daily; ITT – Intention-to-treat; OS – Overall survival; QD – Once daily

Cox proportional hazards time-varying analysis

A Cox proportional hazards time-varying analysis was undertaken to allow for adjustment of clinically relevant covariates and their change over time to estimate an effect on survival. Comparison of ripretinib BID vs QD resulted in a HR of 1.37 (95% CI 0.66 - to 2.84; $p=0.397$) indicating a 37% increase in the risk of death after dose escalation.⁷⁹

Although not statistically significant, this suggests IPDE has a negative impact on survival, which may be perceived as counterintuitive.⁷⁹ This approach avoids the risk of potential bias associated with the BID-censored analysis described; however, the primary limitation in quantifying the effect of dose escalation is not being able to adjust for all possible treatment effect modifiers or outcome predictors. This is due to the fact randomisation was broken after the first incidence of disease progression in the trial; all possible treatment effect modifiers and outcome predictors were not recorded at this point. The resulting potential for selection and survivor bias makes it difficult to Company evidence submission template for ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments (review of TA881) [ID6496]

attribute differences in the risk of death directly to the dosing regimen rather than to underlying unmeasured health status factors.

Two-stage adjustment

A 2-stage modelling approach was used to estimate the effect of patients switching to BID dosing rather than continuing with QD dosing. Only patients randomised to ripretinib QD were included (n=85) in the model, since patients randomised to placebo could only switch to BID dosing after switching from placebo to QD dosing. In stage 1, analysis of OS data using various distributions (exponential, Weibull, log-normal, log-logistic, and generalised gamma) and simple or complex covariate adjustment were fitted to obtain acceleration factors and time ratios. In all cases, time ratios were >1 which indicated prolonged survival for patients that switched to BID compared with patients who remained on QD dosing. Complex covariate adjustment resulted in survival time ratios of 1.94 to 2.72.

The 2-stage method assumes that there is no time-dependent confounding between the time of progression and the time of treatment switch; as the difference between the two was generally small, this was felt to be true. However, the Cox proportional hazards time-varying analysis showed a lack of alignment in these results, raising questions over the certainty of this assumption and the associated result.

Inverse probability of censoring weighting (IPCW) adjustment

IPCW was considered as a method for assessing treatment switch from QD to BID dosing, but it was concluded that any results generated would not be reliable or informative. INVICTUS was a small trial (n=129), from a statistical perspective, and only 41 of the 85 ripretinib arm patients did not switch from QD to BID (the 'control group'). As such, it is likely that any results would have wide confidence intervals. Given the two analyses described above, it was felt that a further analysis would not give useful insights.

UK clinical advisory board

Clinical opinion was sought regarding the effect of dose escalation vs remaining on QD dosing after disease progression. Although clinicians agreed the effect was not negligible, it was perceived that it could not be quantified based on the available data. Ultimately clinicians felt that IPDE was unlikely to have changed the shape of the survival curve. Rather, it was deemed likely that long-term survivors, who support the end of survival curves, were likely to have less aggressive disease that progresses more slowly, irrespective of whether the patient receives QD or BID dosing.¹⁸

Conclusions

These analyses demonstrate the uncertainty surrounding the impact of ripretinib dose escalation on OS in INVICTUS, given the considerable variability in the magnitude of and the positive or negative nature of the effect (Table 15). A reasonable explanation as to why the statistical methodologies give differing results, with no clear trend, is the limitations in the available data. Appropriate adjustment for imbalances would require that all prognostic and treatment effect modifiers are collected at the time of potential treatment switch. Given the variability in the results, it is likely that a key factor driving the choice to dose escalate was not captured.

Adjusting the OS curve for crossover to BID dosing in the economic model presents a significantly more complex scenario compared with adjusting for placebo crossover. The challenge is that not only had patients in the ripretinib arm switched to BID dosing; but some placebo-treated patients had already switched to active treatment before switching to BID dosing. To our knowledge, there is no established, commonly used statistical framework that provides robust and reliable estimates when adjusting for patients who switch treatment twice (placebo to QD and then to BID ripretinib). Theoretically, formal adjustment of multiple switches may be feasible in trials with sufficiently large sample size; this is less likely to be an option for smaller clinical trials concerning rare diseases.

Table 15: Summary of analyses quantifying the effect of IPDE on OS

Analysis	Effect of dose escalation	Considerations
Open-label BID vs QD OS analysis ⁶⁶	Considerable (+4.5 months median OS), positive effect	Likely overestimated effect for BID in the absence of adjustment for treatment effect modifiers, specifically ECOG PS
BID censoring analysis ⁷⁸	Negligible, negative effect	Result is likely to include bias associated with informative censoring and loss of data over time
Cox proportional hazards time-varying analysis ⁷⁹	Considerable (40% increase in risk of death), negative effect	Does not seem clinically realistic given the safety profile of BID dosing; suggests that another (uncontrollable) treatment effect modifier drove the choice to dose escalate
Two-stage adjustment	Uncertain, positive effect	Assumes no time-dependent confounding between time of progression and time of treatment switch
IPCW	n/a	Patient numbers considered too small statistically to give informative results
Clinicians (UK advisory board) ¹⁸	Unquantifiable, positive effect	Available data are insufficient to estimate effect size

Abbreviations: BID - twice-a-day ripretinib; ECOG PS - Eastern Cooperative Oncology Group performance status; IPCW - Inverse probability of censoring weighting; OS - overall survival; QD – once-a-day ripretinib

Importantly, the clinician advisory board felt that IPDE was unlikely to have shifted the shape of the survival curve, with long-term survivors being likely to survive irrespective of dose due to inherent differences in disease characteristics.¹⁸

It should be emphasized that, across the ITT population, 75.9% of ripretinib exposure time was with QD dosing, with the remaining 24.1% being accounted for by BID dosing, with BID dosing restricted until after first disease progression. This suggests

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that the benefit of ripretinib in INVICTUS was primarily driven by QD dosing. Given this, and the results of the above analyses, the ITT OS data without adjustment for BID dosing have been included in the base case cost-effectiveness model to avoid the introduction of additional uncertainty. However, some of the analyses described were included as scenarios to assess any possible impact on cost-effectiveness (see Sections 3.3.2 and 3.11.3).

ORR – secondary endpoint

In the ripretinib group, 9.4% (n=8; 95% CI 4.2% to 17.7%; p=0.0504) of patients had a confirmed ORR as assessed by BICR in the double-blind analysis period, compared with no patients in the placebo group (Table 16). Although ORR did not reach statistical significance it was considered of clinically meaningful benefit to patients, with ripretinib demonstrating favourable disease control. A higher proportion of patients who received ripretinib had stable disease compared with those on placebo at 6 weeks (66% vs 20%) and at 12 weeks (47% vs 5%).¹⁵

Table 16: ORR as assessed by BICR at 6 weeks (ITT population)

Response	Ripretinib (n=85)		Placebo (n=44)		P-value *
	n (%)	95% CI	n (%)	95% CI	
Confirmed ORR	8 (9%)	4% to 18%*	0 (0%)	0% to 8%*	0.0504
CR	0 (0%)	0% to 4%	0 (0%)	0% to 8%	-
PR	8 (9%)	4% to 18%	0 (0%)	0% to 8%	-
SD (6 weeks)	56 (66%)	55% to 76%	9 (20%)	10% to 35%	-
SD (12 weeks)	40 (47%)	36% to 58%	2 (5%)	1% to 16%	-
PD	16 (19%)	11% to 29%	28 (64%)	48% to 78%	-
Not evaluable	4 (5%)	-	3 (7%)	-	-
No response assessment	1 (1%)	-	4 (9%)	-	-

Abbreviations: BICR - Blinded independent central review; CI - Confidence interval; CR - Complete response; ITT - intent-to-treat; OR - Objective response; ORR - Objective response rate; PD - Progressive disease; PR - Partial response; SD - Stable disease.

* p-value is based on Fisher's exact test.

Source: Blay et al. 2020,¹⁵

Fewer patients in the ripretinib group had progressive disease than in the placebo group (19% vs 64%).¹⁵ Importantly, absence of disease progression is considered a

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marker of therapeutic benefit in patients with GIST and is predictive of PFS and OS benefit.^{80,81}

In subsequent analyses after an additional 9 and 19 months of follow-up, ORR rates were 11.8% (95% CI 5.8% to 20.6%) in the ripretinib group vs 0% (95% CI 0% to 8.0%) in the placebo group.^{23,65}

Other secondary endpoints

The secondary endpoints of DOR, TTP, and time to best response were not included in the statistical hierarchy due to insufficient power. The results reported are therefore considered descriptive and are not tested for statistical significance.¹⁵

As of 31 May 2019, median time to best response was 1.9 months (IQR 1.0 to 2.7) with ripretinib, with no patients in the placebo group achieving a response. Responses in patients treated with ripretinib were durable, with median DOR not reached at the primary data cut-off; by the time of the January 2021 data cut-off, median DOR was 14.5 months.^{15,23}

Median TTP was longer in the ripretinib group (6.4 months [95% CI 4.6 to 8.4]) vs the placebo group (1.0 month [95% CI 0.9 to 1.7]).¹⁵ A TTP event occurred in 54.1% of patients (n=46, 39 censored) in the ripretinib group compared with 72.7% (n=32; 12 censored) in the placebo group.⁵¹

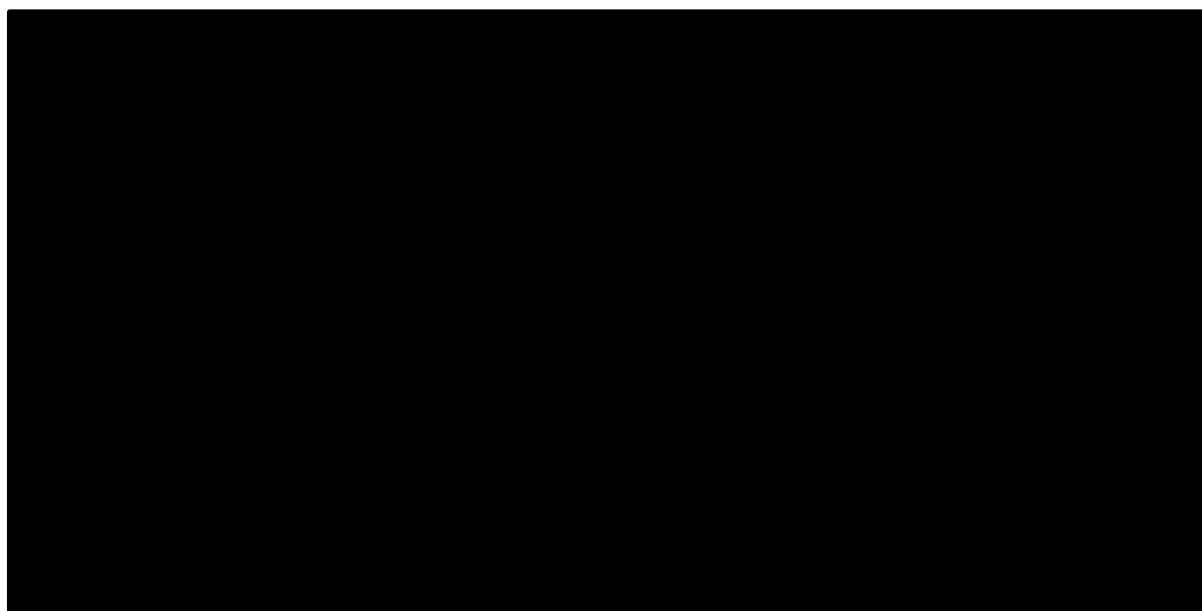
These results indicate durable, clinically meaningful disease control for ripretinib treatment compared with placebo.

TTD (post hoc analysis)

As of 15 January 2021, median TTD for ripretinib (any dose) during the double-blind and open-label periods was ■■■ considering patients randomised to ripretinib (Figure 13).⁷² Comparison of median TTD with median PFS (6.3 months [95% CI 4.6 to 8.1 months]) indicated that on average patients remained on ripretinib for ■■■ months after radiological progression (Figure 13). Of patients randomised to the ripretinib arm, 74% entered the open-label period to continue ripretinib.^{15,72} The proportion of patients remaining on treatment after progression and the duration of treatment beyond progression reflected that expected in UK clinical practice.^{15,69} Clinicians at a UK Company evidence submission template for ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments (review of TA881) [ID6496]

advisory board stated that they would expect approximately 80% of patients to remain on ripretinib treatment post-progression and that there is no reason why treatment beyond progression would differ from that seen in INVICTUS; study data were deemed similar to those from the Royal Marsden expanded use program (Section 2.6.3).³⁸ The median duration of treatment with ripretinib 150 mg BID was 3.7 months (range: 1 day to 18.6 months) and 11 of 43 patients (26%) were treated at this dose for 6 months or longer.⁶⁶

Figure 13: TTD Kaplan-Meier curve for patients randomised to ripretinib in INVICTUS



Abbreviations: CI – Confidence interval; TTD – Time-to-discontinuation.
Source: Deciphera Pharmaceuticals Data on File. Ripretinib post hoc TTD analysis. 25 July 2024 ⁷²

HRQoL

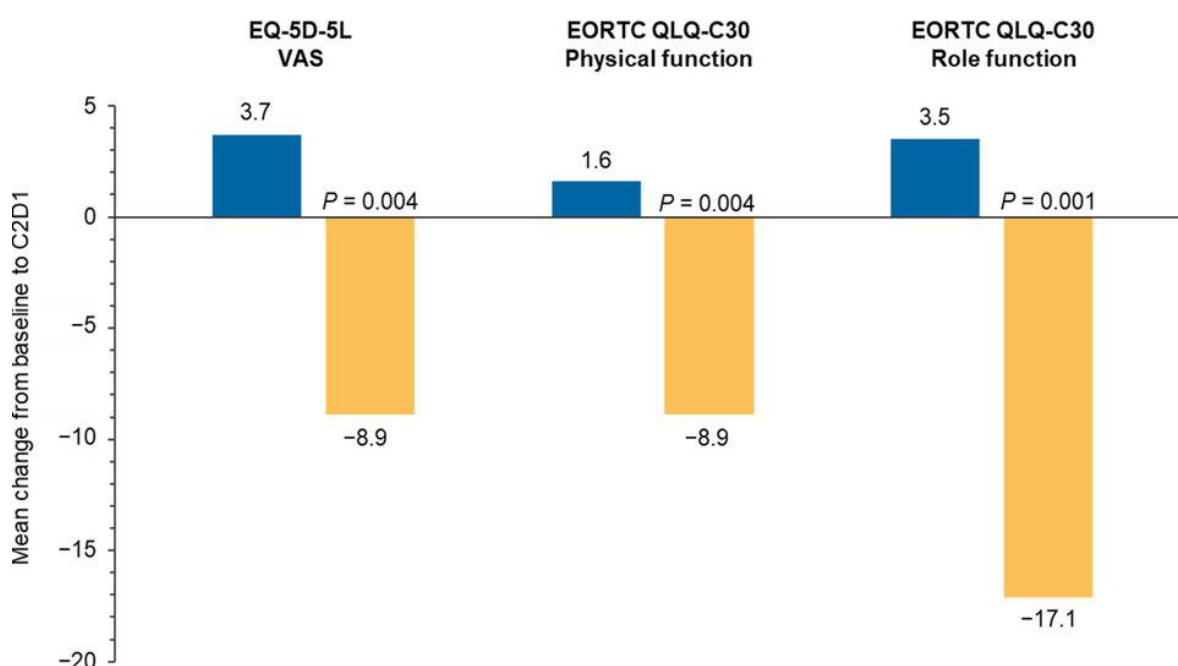
As ORR did not reach statistical significance, HRQoL results could not be formally tested for statistical significance owing to the hierarchical nature of the testing procedures.¹⁶ The results reported are descriptive and statistical significance is not implied.

HRQoL in INVICTUS was assessed using the EORTC QLQ-C30 role and physical functioning domains, EQ-5D-5L and EQ-VAS from baseline to Cycle 2 Day 1. On Cycle 2 Day 1, 71 patients were evaluable in the ripretinib arm and 32 patients were evaluable in the placebo arm; on Cycle 3 Day 1, 61 patients were evaluable in the Company evidence submission template for ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments (review of TA881) [ID6496]

ripretinib arm and 13 patients were evaluable in the placebo arm. Comparisons were only made to Cycle 2 Day 1 due to the small number of patients in the placebo group after this time point.¹⁶

Patients in the ripretinib group reported an improvement in physical and role functioning domains of EORTC QLQ-C30 from baseline to Cycle 2 Day 1, with an adjusted mean increase in scores (indicating improvement) of 1.6 and 3.5, respectively; a decline of 8.9 and 17.1 was seen for patients in the placebo group.¹⁶ Patients receiving ripretinib reported an improvement in HRQoL from baseline to Cycle 2 Day 1, as assessed by an adjusted mean increase in EQ-VAS scores of 3.7 vs a decline of 8.9 with placebo. These differences in PRO measures between patients receiving ripretinib and those receiving placebo were considered clinically significant using a previously defined minimal clinically important difference (MCID),⁸² and p-values were significant.¹⁵ A >10% mean score change or score change of 5 points was considered the threshold to determine a MCID.¹⁶ Based on this definition, treatment with ripretinib led to a clinically meaningful benefit compared with placebo across PRO measures (Figure 14 and Table 17).

Figure 14: Change from baseline to Cycle 2 Day 1 in EQ-VAS and EORTC QLQ-C30 PRO measures (ITT population)



Legend: Ripretinib (Blue), Placebo (Yellow)

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Abbreviations: C2D1 - Cycle 2, Day 1; EORTC QLQ-C30 - European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-item; EQ-VAS - EuroQol visual analogue scale; ITT - Intent-to-treat; PROM - Patient-reported outcome measure.

Note: p-values are nominal.

The physical and role function questions were rolled up to a score out of 100. Change from baseline to C2D1 in EQ-VAS scores were evaluable in 70 and 32 patients in the ripretinib and placebo arm, respectively. For the EORTC QLQ-C30 physical functioning, 71 and 32 patients were evaluable in each group, respectively, and for the EORTC QLQ-C30 role functioning, 70 and 32 patients were evaluable in each group, respectively.

Source: Schöffski et al. 2022,¹⁶

Table 17: Change from baseline to Cycle 2 Day 1 in HRQoL measures

	Ripretinib (n=85)	Placebo (n=44)
EORTC QLQ-C30*		
<i>Role Functioning</i>		
Baseline, mean (SD; 95% CI)	n=74	n=42
	69.4 (30.1; 62.4 to 76.3)	73.8 (30.4; 64.3 to 83.3)
C2D1, mean (SD; 95% CI)	n=79	n=33
	75.1 (26.1; 69.3 to 81.0)	65.2 (27.8; 55.3 to 75.0)
Change from baseline, adjusted mean (95% CI)	n=70	n=32
	3.5 (-3.4 to 10.5)	-17.1 (-27.0 to -7.1)
Treatment difference (95% CI)	20.6 (8.6 to 32.6)	
<i>Physical Functioning</i>		
Baseline, mean (SD; 95% CI)	n=74	n=42
	75.7 (21.6; 70.7 to 80.7)	76.0 (26.5; 67.8 to 84.3)
C2D1, mean (SD; 95% CI)	n=80	n=33
	79.4 (17.3; 75.5 to 83.3)	75.2 (20.2; 68.0 to 82.3)
Change from baseline, adjusted mean (95% CI)	n=71	n=32
	1.6 (-2.5 to 5.7)	-8.9 (-14.8 to -3.0)
Treatment difference (95% CI)	10.5 (3.4 to 17.6)	
EQ-5D-5L		
<i>EQ-VAS, overall health</i>		
Baseline, mean (SD; 95% CI)	n=74	n=42
	63.9 (22.1; 58.8 to 69.0)	65.6 (22.9; 58.5 to 72.8)
C2D1, mean (SD; 95% CI)	n=78	n=33
	69.5 (20.5; 64.9 to 74.2)	64.1 (23.3; 55.9 to 72.4)
Change from baseline, mean (SD; 95% CI)	n=70	n=32
	3.7 (20.4; -1.1 to 8.6)	-8.9 (19.3; -15.9 to -1.9)

Abbreviations: C2D1 - Cycle, 2 day; CI: Confidence interval; EORTC QLQ-C30 - European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-item; EQ-VAS - EuroQol visual

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analogue scale; EQ-5D-5L - EuroQol 5 dimensions 5 levels; HRQoL - Health-related quality-of-life; ITT - Intent-to-treat; SD - Standard deviation.

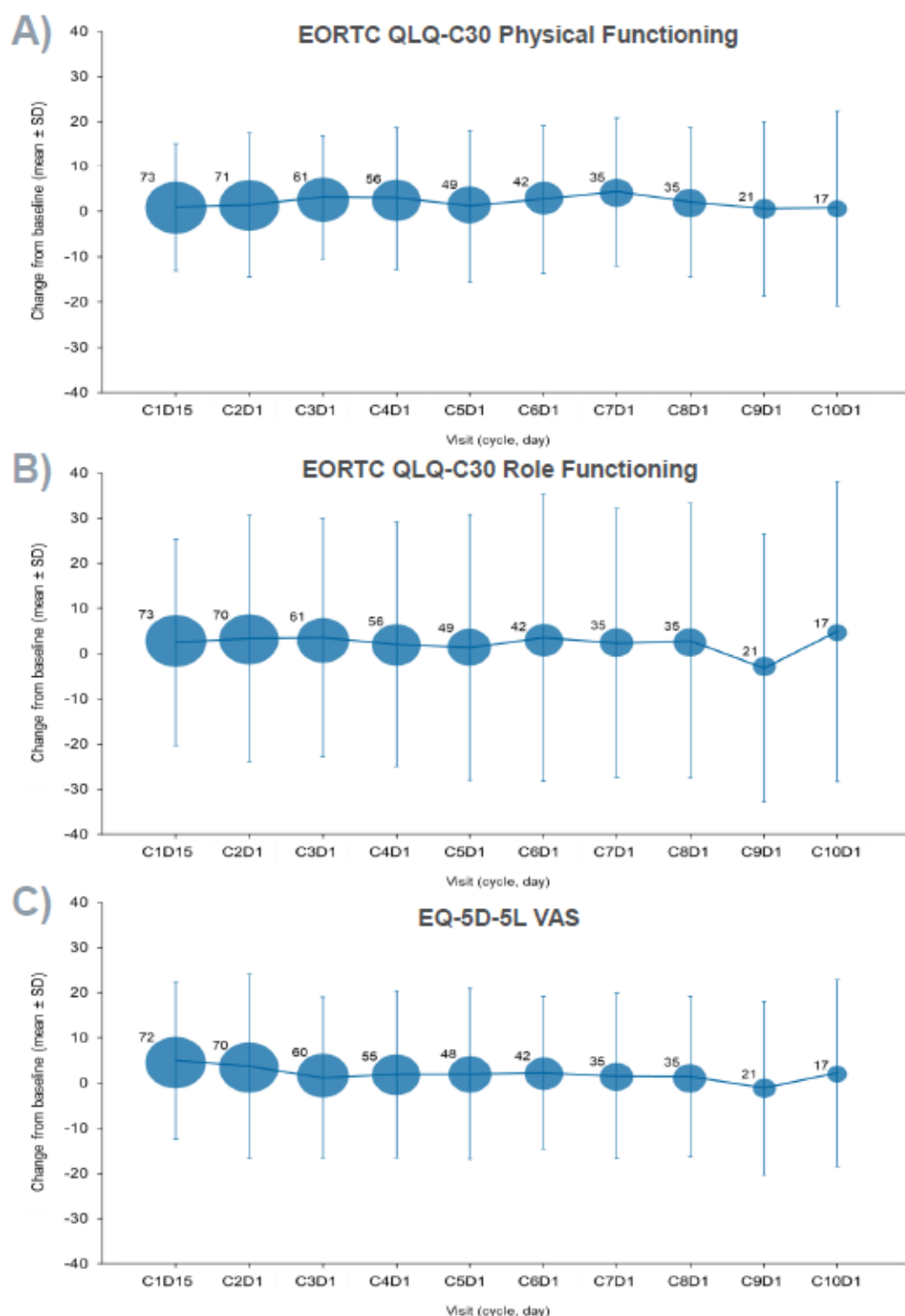
* Either a >10% mean score change or score change of 5 points was considered the minimally important clinical difference.

Source: Blay et al. 2020,¹⁵

Patient demographic and baseline characteristics were generally well balanced between treatment arms, in terms of stratification factors including ECOG status and number of prior systemic anticancer treatments.⁸³ Adjusted mean change from baseline to Cycle 2 Day 1 in utility scores was -0.009 (standard error 0.020) for the ripretinib group and -0.06 (standard error 0.028) for the placebo group.^{83,84}

When considering change over time, patients treated with ripretinib showed a stabilisation in score for all PRO measures through to Cycle 10, as shown in Figure 15. This indicates that patients were able to maintain QoL and function for approximately 8 months with ripretinib, beyond the median PFS (6.3 months); patients in the placebo arm showed a significant decline in PRO measures after 1 month (Figure 14).¹⁶

Figure 15: Longitudinal change in PRO scores in the ripretinib 150 mg QD group (ITT population)



Abbreviations: EORTC QLQ-C30 - European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-item; EQ-5D-5L VAS - EuroQol 5 dimensions 5 levels visual analogue scale; ITT -Intent-to-treat; PRO - Patient-reported outcome; QD - Once a day.

Note: the size of the blue dot is proportional to number of patients.

Source: Schöffski et al. 2022.¹⁶

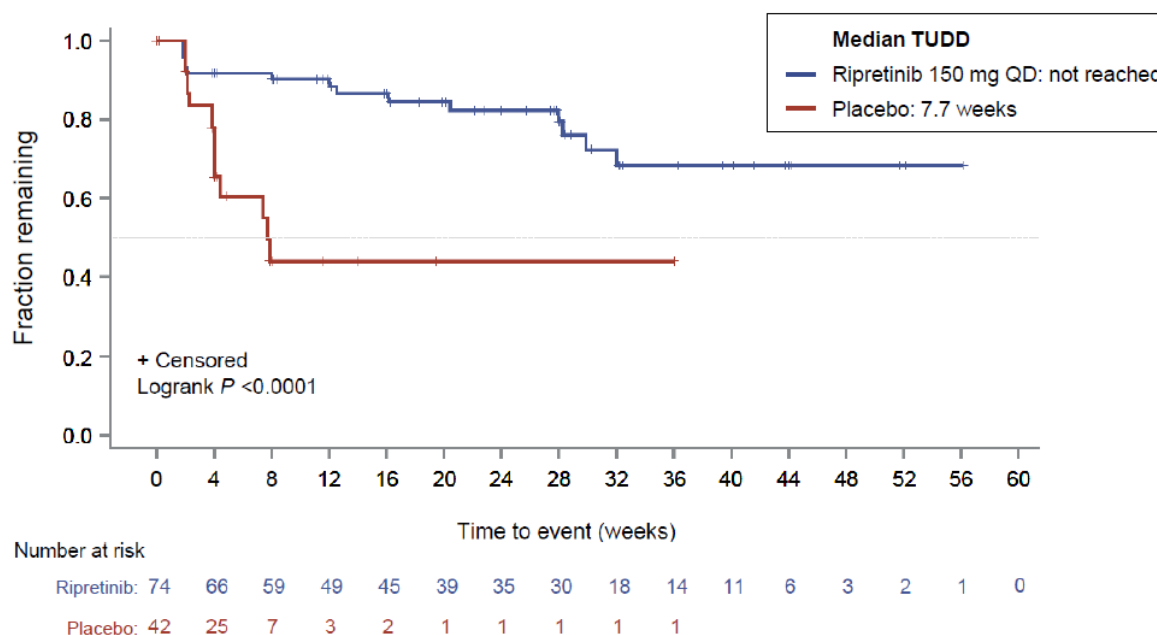
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Exploratory analysis indicated that for patients in the ripretinib group who experienced alopecia, a commonly reported treatment-emergent adverse event (TEAE), HRQoL was maintained; repeated measures analysis demonstrated that overall health, physical function, and role function were maintained over time for patients receiving ripretinib irrespective of whether they had alopecia or not.⁶¹

Time until definitive deterioration

Patients receiving ripretinib reported longer TUDD in all assessed PRO measures (a clinically meaningful decline in the PRO measure that does not recover based on a data cut-off of August 2020) compared with those receiving placebo.⁵⁶ This was seen for each EQ-VAS PRO measure, physical and role functioning (measured jointly), overall health, and overall QoL on EORTC QLQ-C30. For overall health, median TUDD for the placebo group was 7.7 weeks but had not been reached in the ripretinib group by 56 weeks (Figure 16). For physical and role function (EORTC QLQ-C30) and EQ-VAS score, median TUDD was 41.6 weeks in the ripretinib group vs 7.9 weeks in the placebo group (Figure 17 and Figure 18). Median TUDD was longer than median PFS (6.3 months) and median TTD (8.8 months) with ripretinib, suggesting that tolerability did not drive treatment discontinuation and that HRQoL was maintained after disease progression.⁵⁶

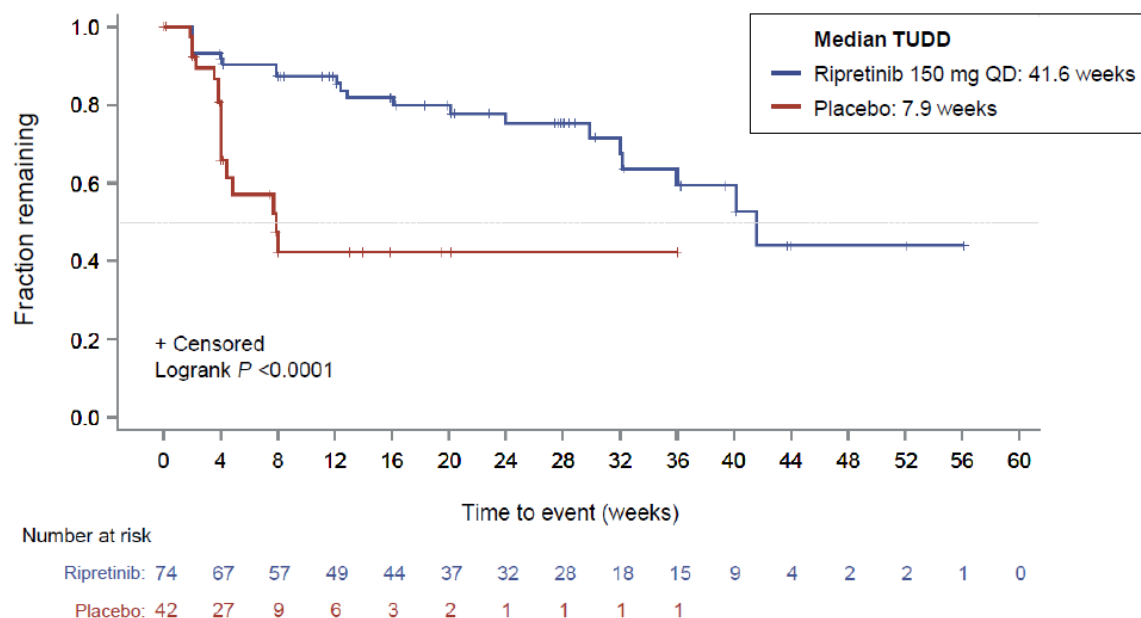
Figure 16: TUDD for EORTC QLQ-C30 overall health and QoL



Abbreviations: EORTC QLQ-C30 - European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire; QD - Once daily; QoL - Quality-of-life; TUDD - Time until definitive deterioration.

Source: Becker et al. 2021⁵⁶

Figure 17: TUDD for EORTC QLQ-C30 physical and role functioning

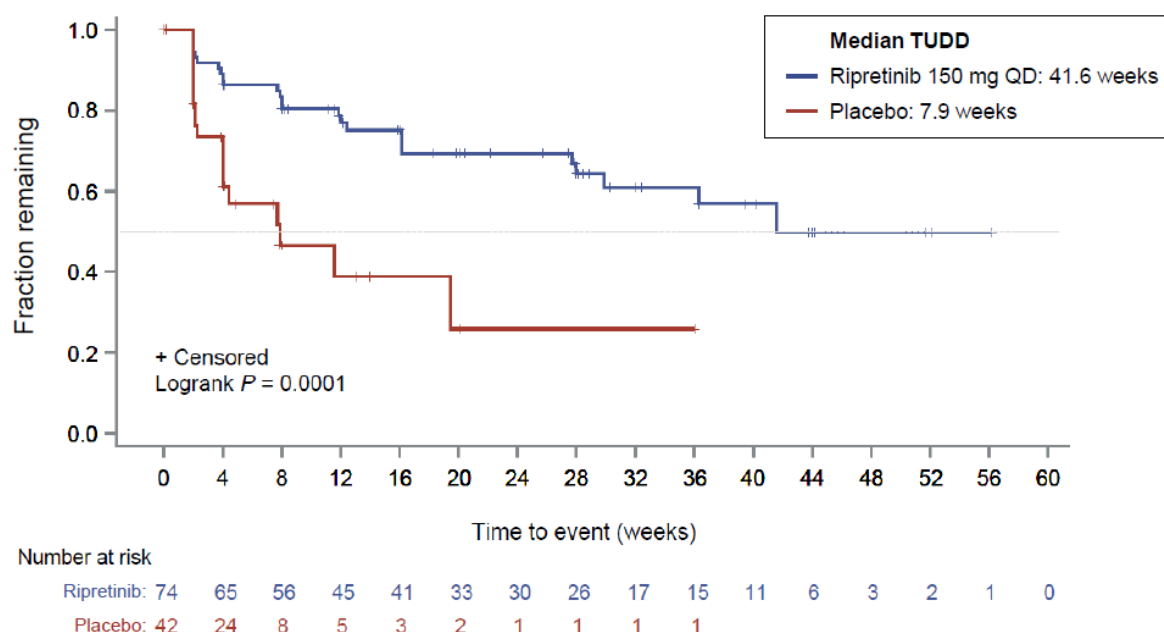


Abbreviations: EORTC QLQ-C30 - European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire; QD - Once daily; TUDD - Time until definitive deterioration.

Source: Becker et al. 2021⁵⁶

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Figure 18: TUDD for EQ-5D-5L VAS score



Abbreviations: EQ-5D-5L - 5-Level EuroQol-5 Dimension; QD - Once daily; TUDD - time until definitive deterioration; VAS - Visual analogue scale.

Source: Becker et al. 2021⁵⁶

2.6.3 Royal Marsden expanded access program

Patient disposition

The median follow-up time in the overall patient population was 24.2 months (95% CI 19.7–29.7). At the time of data cut-off, 5 (11.1%) patients were still receiving 150 mg ripretinib QD. Ripretinib QD was discontinued for the remaining 40 patients for the following reasons: mRECIST PD in 21 (46.7%) cases, clinical PD in 17 (37.8%) cases, and toxicity in 2 (4.4%) cases. Of the 21 patients with mRECIST PD, 15 dose-escalated to ripretinib BID and 6 did not dose-escalate (2 received another TKI, and 4 declined IPDE and were referred back to their local team). Of the 17 patients with clinical PD, 10 were too unwell to continue treatment and 7 dose-escalated to ripretinib BID. In total, 22 (48.9%) patients had their dose escalated to ripretinib BID.⁶⁹

Of the 22 patients undergoing IPDE, 4 (18.2%) were still receiving ripretinib BID at the time of data cut-off, 4 (18.2%) had clinical progression and 14 (63.6%) had mRECIST

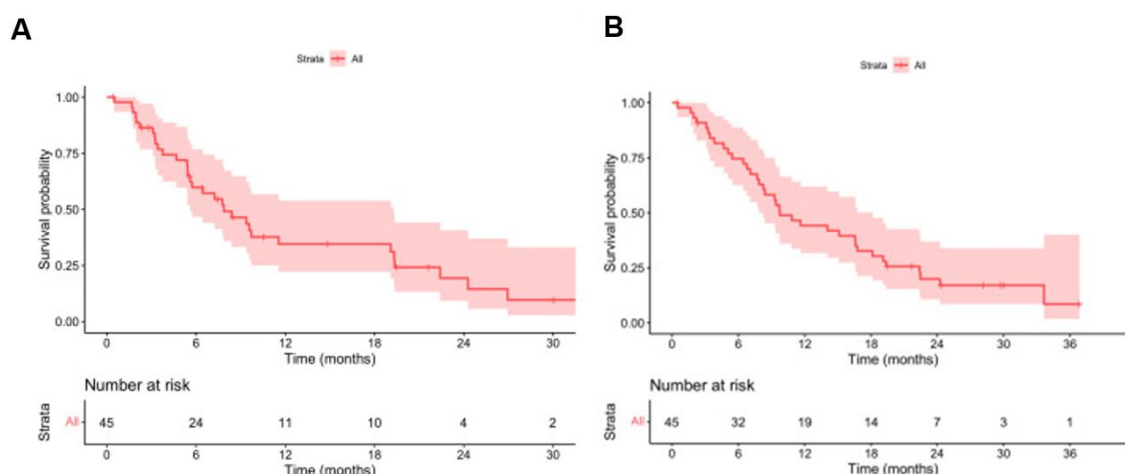
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PD. Four patients went on to receive a further line of treatment after progression on ripretinib BID. At the time of data cut-off, 20 (44.4%) patients were still alive and 25 (55.6%) had died.⁶⁹

Progression free survival

The median PFS for patients receiving ripretinib QD was 7.9 months (95% CI 5.6–19.3) (Figure 19A). The median PFS for patients receiving ripretinib BID (after initial disease progression) was 5.4 months (95% CI 2.8–9.3).⁶⁹ Similar to INVICTUS, the PFS from dose escalation to disease progression on that dose was shorter compared with PFS after initial treatment with ripretinib (median PFS2/PFS1 ratio in INVICTUS was 80%).^{66,69} The median PFS achieved in INVICTUS (6.3, 95% CI 4.6 to 8.1, months) is shorter than the median PFS for patients receiving ripretinib QD during the expanded access program, potentially due to the lower frequency of radiological assessment in clinical practice.¹⁸ In the overall study population, median PFS ITT was 9.7 (95% CI 8.3–18.1) months, i.e., 9.7 months from the first ripretinib QD dose to disease progression if patients did not undergo IPDE or time until progression on ripretinib BID dosing for those who did (Figure 19B).⁶⁹

Figure 19: (A) Median PFS ripretinib QD (B) Median PFS ripretinib, ITT population, UK expanded access program



Abbreviations: ITT – Intention-to-treat, PFS – Progression-free survival, QD – Once daily, UK – United Kingdom
Source: Lim et al. 2024.⁶⁹

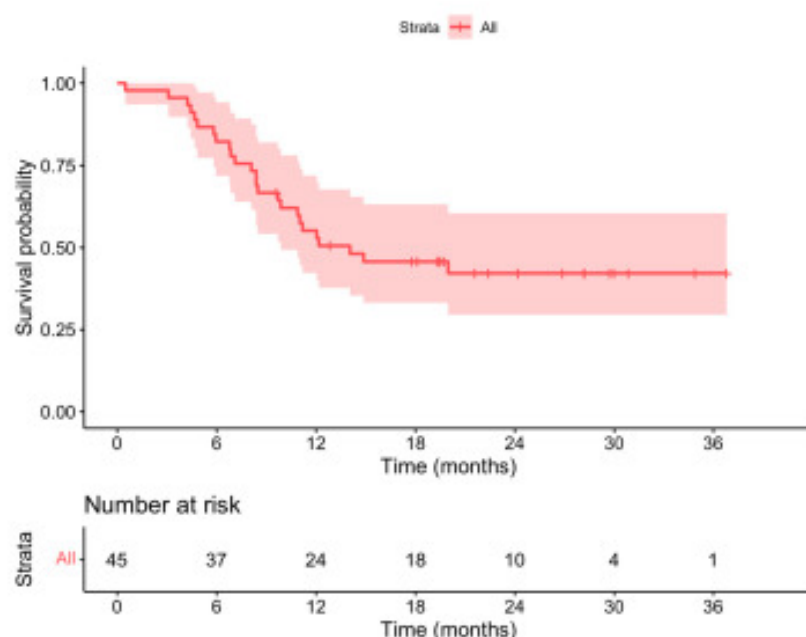
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Overall survival

The median OS for the overall study population was 14.0 (95% CI 9.9–NA) months, including all patients, irrespective of post-progression ripretinib dosing (Figure 20).⁶⁹ The median OS achieved in the expanded access program was lower than the median OS achieved in INVICTUS (18.2, 95% CI 13.1 to 30.7, months) after a similar median follow up period.^{15,69} The OS achieved in clinical practice is often lower than that achieved in clinical trials due to the ‘controlled by protocol’ nature of a clinical trial. Stringent recruitment criteria and intensive patient care with close monitoring and contact are maintained throughout a clinical study.⁸⁵ Analysis of cancer clinical trial control arms compared with real-world cohorts showed that poorer outcomes are generally seen in routine clinical practice unless patient populations are carefully aligned/adjusted to ensure consistency.⁸⁶ When consulted, UK clinicians agreed that clinical study populations meet strict inclusion criteria and as a result patients are often fitter than those seen in routine clinical practice.⁶⁹

Consistent with the reasoning above, patients in the expanded access program had poorer performance status at baseline compared those in INVICTUS (ECOG 1-2 98% vs 56%, respectively).^{15,69} UK clinicians confirmed that ECOG is a key treatment effect modifier in this patient population.^{18,46,77,87}

Figure 20: Median OS ripretinib, ITT population, UK expanded access program



Source: Lim et al. 2024.⁶⁹

Objective response rates

Three patients in the expanded access program did not undergo radiologic evaluation whilst receiving ripretinib QD, because of their rapid clinical deterioration. For the 42 patients with at least one radiological evaluation, the best responses to ripretinib QD were PR in 7 patients (16.7%) and SD in 29 patients (69.0%). The median time to best response was 2.6 (IQR 1.9–3.3) months.⁶⁹

Three patients did not undergo radiologic evaluation whilst on ripretinib BID; 2 patients because of rapid clinical deterioration and 1 patient was dose-escalated 2 weeks before data cut-off. In the 20 evaluable patients, the best responses to ripretinib BID were PR in 2 patients (10.0%) and SD in 9 patients (45.0%).⁶⁹

Rates of objective response and SD were comparable to those achieved in INVICTUS at 9% and 66%, respectively.^{15,69}

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An absence of objective response with ripretinib at the $\geq 4L$ of treatment or above does not preclude a clinical benefit in asymptomatic patients, particularly since objective responses are rare with any agent in this clinical setting. Unlike some other advanced solid tumours, an absence of disease progression (whether a PR or SD) is considered an important therapeutic marker of benefit and is predictive of improvements in PFS and OS in patients with advanced GIST.^{66,80,81}

Time-to-discontinuation and treatment-beyond-progression

The median TTD in patients receiving ripretinib QD was similar to their median PFS, at 7.1 (95% CI 5.8–11.0) months.⁶⁹ Ripretinib QD TBP was recorded for 14 patients (31.1%). Patients with TBP generally showed no significant differences in baseline characteristics compared with patients without TBP; the only exception was site of disease and this difference is most likely due to the small sample size. The median duration of TBP was 1.9 months (IQR 1.0–3.0 months).⁶⁹

The median TTD in patients receiving ripretinib BID was similar to their median PFS BID, at 6.5 (95% CI 4.6–10.7) months. Ripretinib BID TBP (defined as ripretinib treatment beyond second disease progression) was observed in 6 patients (27.3%). The median duration of TBP was 2.8 months (IQR 1.0–5.4 months).^{18,69}

The median duration of TBP is comparable to that estimated for the INVICTUS ITT population (■■■■).^{15,72} Clinicians agreed at a UK advisory board that this aligns with their expectations for ripretinib in UK clinical practice.³⁸

2.7 Subsequent treatments used in the relevant studies

Collection of data on subsequent lines of therapy was not prespecified in the study protocol for INVICTUS given ripretinib was being investigated as a $\geq 4L$ treatment option for patients with advanced GIST with no other treatments currently indicated as $\geq 4L$ treatment options in this patient population.

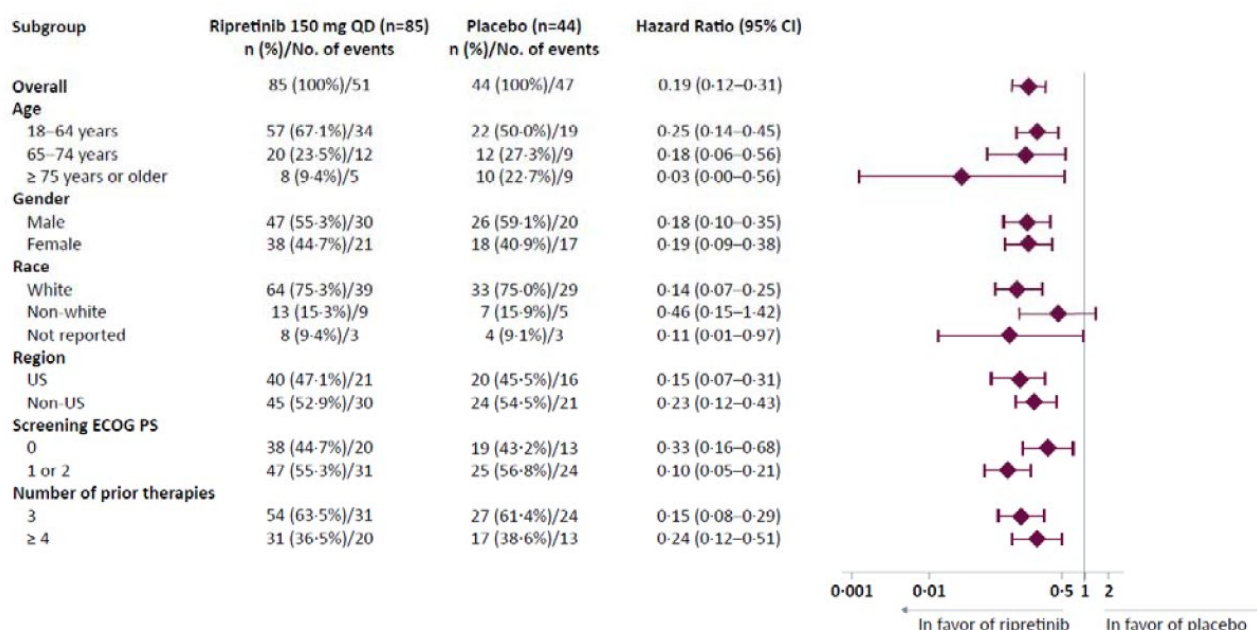
2.8 Subgroup analysis

2.8.1 INVICTUS subgroup analyses

Subgroup analyses for PFS (pre-specified)

PFS outcomes were assessed by subgroup to understand the treatment effect of ripretinib in different patient populations. In terms of HR for PFS, the subgroup analyses consistently favour the experimental arm, as shown in Figure 21, including the stratification groups (ECOG 0 vs 1 or 2) with a HR of 0.33 and 0.10, respectively.¹⁵ The HR values for PFS are similar for 3 prior lines of therapy (HR [CI]: 0.15 [0.08, 0.29]) compared with ≥ 4 prior lines of therapy (HR [CI]: 0.24 [0.12, 0.51]), and confidence intervals overlap. This confirms that there is no significant difference in treatment effect on PFS for patients who have received 3 vs ≥ 4 prior lines of therapy. Furthermore, the HR values for PFS are similar for ages 18-64 years (HR [CI]: 0.25 [0.14, 0.45]) and ages 65-74 years (HR [CI]: 0.19 [0.06, 0.56]), again, with confidence intervals overlapping. The PFS HR value for age ≥ 75 and older is more uncertain due to the small patient numbers. Clinicians consulted at a UK advisory board did not consider age or line of therapy to be treatment effect modifiers.¹⁸ The PFS subgroup analyses for the January 2021 data cut-off shows consistent results with the May 2019 data cut-off.²³

Figure 21: PFS in patient subgroups as assessed by BICR (ITT population; 31 May 2019 data cut-off)



Abbreviations: BICR - Blinded independent central review; CI - Confidence interval; ECOG PS - Eastern Cooperative Oncology Group Performance Status; ITT - Intent-to-treat; PFS - Progression-free survival; QD - Once a day.

Note: The number (% of total patients) of patients in each treatment group along with the number of events for each subgroup is presented.

Source: Blay et al. 2020.¹⁵

Subgroup analyses for OS (post hoc)

Subgroup analyses for OS by age and line of treatment are shown in Table 18 (data cut-off 15 January 2021).

Table 18: Subgroup analyses for OS, 15 January 2021 cut-off

Subgroup	Ripretinib vs placebo HR (95% CI)
Age	
18 – 64 years	0.42 (0.23-0.75)
65 – 74 years	0.46 (0.19-1.08)
75 years or older	0.41 (0.13-1.31)
Number of prior therapies	
3 prior therapies (n=54)	0.31 (0.18-0.54)
≥ 4 prior therapies (n=31)	0.63 (0.31-1.29)

Abbreviations: CI - Confidence interval; HR - Hazard ratio.

Source: NICE, Technology appraisal guidance [TA881], committee papers (unredacted)²⁰

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OS was comparable across age groups. OS was numerically more favourable for patients with 3 prior therapies than those with ≥ 4 prior therapies; however, confidence intervals overlapped indicating no significant difference in OS between the two groups.²⁰

Subgroup analyses for ORR (post hoc) are included in Appendix C.

2.8.2 Royal Marsden expanded access program: subgroup analyses

In multivariate Cox regression models, the absence of a KIT exon 11 mutation was associated with a statistically significant reduction in PFS QD (HR 4.67, 95% CI 1.53–14.29), PFS ITT (HR 3.06, 95% CI 1.08–8.67) and OS (HR 4.19, 95% CI 1.49–11.82) compared to when a KIT exon 11 mutation is present.⁶⁹ Furthermore, patients with three or more metastatic sites also had statistically shorter PFS ITT compared with patients with less than two metastatic sites (HR 3.00, 95% CI 1.05–8.57). Other variables tested, including number of previous lines of treatment (2 vs 3 or more) and age, were not associated with significant differences in PFS (QD or ITT) or OS, (Appendix C).⁶⁹ This is consistent with the INVICTUS OS subgroup analyses for age and number of previous lines of therapy.

2.9 Meta-analysis

Not applicable.

2.10 Indirect and mixed treatment comparisons

Not applicable.

2.11 Adverse reactions

2.11.1 INVICTUS adverse reactions

INVICTUS involved safety analyses conducted in the safety population during the double-blind period.¹⁵ The safety population was defined as all patients who received at least one dose of study drug and included all 85 patients randomised to ripretinib

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150 mg QD and 43 out of the 44 patients randomised to placebo (128 in total).¹⁵ One patient randomised to placebo did not receive treatment.¹⁵

Treatment emergent adverse events

Ripretinib was generally well-tolerated and associated with an acceptable safety profile in INVICTUS. The overall frequency of TEAEs was similar between the ripretinib and placebo groups (99% [84] vs 98% [42]).⁶²

At the January 2021 data cut-off, approximately half of patients in the ripretinib group experienced a grade 3 or 4 TEAE (49.4%) and 8% experienced a TEAE leading to treatment discontinuation.²³ Grade 3 or 4 TEAEs and TEAEs leading to discontinuation were reported in a similar proportion of patients in the placebo group (44.2% and 12%, respectively).²³ Grade 3 or 4 TEAEs occurring in more than 5% of patients (anaemia, abdominal pain and hypertension) were included in the economic model.

Overall, rates of discontinuation, dose reduction and dose interruption due to TEAEs were similar between the ripretinib and placebo groups. Table 19 and Table 20 provide a summary of TEAEs occurring in INVICTUS.

Table 19: Summary of grade 3/4 TEAEs and dose modifications in the double-blind phase (safety population; 15 January 2021 data cut-off)

Categories	Ripretinib (n=85), n (%)	Placebo (n=43)*, n (%)
Any grade 3/4 TEAE (>3%)		
Anaemia	9 (11%)	6 (14.0%)
Abdominal Pain	6 (7%)	2 (5%)
Hypertension	6 (7%)	0
Hypophosphataemia	4 (5%)	0
Lipase increased	4 (5%)	0
Fatigue	3 (4%)	1 (2%)
Nausea	3 (4%)	0
Vomiting	3 (4%)	0
Any TEAEs leading to dose interruption	24 (28%)	10 (23%)

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Categories	Ripretinib (n=85), n (%)	Placebo (n=43)*, n (%)
Any TEAEs leading to dose reduction	8 (9%)	1 (2%)
Any TEAE leading to treatment discontinuation	7 (8%)	5 (12%)
Any TEAEs leading to death	6 (7)	10 (23%)

Abbreviations: TEAE - Treatment-emergent adverse event.

* 44 patients randomised to placebo; one did not receive treatment.

Source: von Mehren, et al. 2021.²³

Ripretinib was well-tolerated among patients who dose escalated, during both the 150 mg QD and BID dose periods (Table 20).

Table 20: Treatment-emergent adverse events reported in ≥30% of patients with advanced GIST receiving ripretinib in the QD period and the corresponding TEAEs post IPDE to 150 mg BID (10 August 2020 data cut-off)

Categories	Ripretinib 150 mg QD period (n=43), n (%)		Ripretinib 150 mg BID period (n=43), n (%)*	
	All grades	Grade 3/4	All grades	Grade 3/4
Alopecia	26 (60%)	-	6 (14%)	-
Fatigue	19 (44%)	1 (2%)	7 (16%)	2 (5%)
Abdominal pain	18 (42%)	2 (5%)	13 (30%)	3 (7%)
Constipation	16 (37%)	0	8 (19%)	0
Myalgia	15 (35%)	1 (2%)	7 (16%)	0
Decreased appetite	13 (30%)	1 (2%)	11 (26%)	2 (5%)
Nausea	13 (30%)	1 (2%)	10 (23%)	1 (2%)

- indicates where no data were captured regarding adverse event grade ratings

*Data represent new or worsening TEAEs in the ripretinib 150 mg b.i.d. period. The ongoing TEAEs from the ripretinib 150 mg QD period were not included if they remained at the same or lower grade

Source: Zalcborg, et al. 2021,⁶⁶

Treatment emergent serious adverse events

At primary analysis, treatment-emergent serious adverse events (SAEs) were reported in 31% and 44% of patients in the ripretinib and placebo groups, respectively (Table 21).⁶²

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Table 21: Summary of any serious TEAEs in the double-blind phase (safety population; 31 May 2019 data cut-off)

Categories	Ripretinib (n=85), n (%)	Placebo (n=43)*, n (%)
Any treatment-emergent SAE (>2%) ⁶²	26 (31%)	19 (44%)
Abdominal Pain	4 (5%)	2 (5%)
Anaemia	3 (4%)	1 (2%)
Death	3 (4%)	4 (9%)
Nausea	2 (2%)	0
Vomiting	2 (2%)	0

Abbreviations: SAE - Serious adverse event; TEAE - Treatment-emergent adverse event.

* 44 patients randomised to placebo; one did not receive treatment.

Source: von Mehren et al. 2019⁶²

Treatment emergent adverse events of special interest

Incidence of AEs of special interest (AESI) are presented in Table 22.

Table 22: Treatment-emergent adverse events of special interest in the double-blind period (safety population; 31 May 2019 data cut-off)

Preferred term	Ripretinib (n=85), n (%)	Placebo (n=43)*, n (%)

* 44 patients randomised to placebo; one did not receive treatment.

Source: Deciphera Pharmaceuticals. DOF: ripretinib CSR. 2019¹⁹

Treatment-related TEAEs

The most common treatment-related TEAEs (≥20%) among the 85 patients with GIST treated with Company evidence submission template for ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments (review of TA881) [ID6496]

ripretinib were alopecia (49%), myalgia (28%), nausea (26%), fatigue (26%), and PPES (21%).¹⁵ The majority were grade 1 or 2 in severity.¹⁵ PPES occurred exclusively in patients treated with ripretinib and all events were grade 1 (11 [13%] of 85 patients) or grade 2 (seven [8%] patients).¹⁵

The most common (>2%) grade 3 or 4 treatment-related TEAEs in the ripretinib arm were lipase increase (5% of 85 patients), hypertension (4%), fatigue (2%), and hypophosphataemia (2%). In the placebo group, the most common (>2%) grade 3 or 4 treatment-related TEAEs were anaemia (7% of 43 patients), fatigue (2%), diarrhoea (2%), decreased appetite (2%), dehydration (2%), hyperkalaemia (2%), acute kidney injury (2%), and pulmonary oedema (2%).¹⁵

Table 23 lists treatment-related TEAEs ≥10% in the ripretinib group compared to the placebo group.¹⁵

Table 23: Treatment-related TEAEs in ≥10% of patients in the ripretinib group compared to placebo – double-blind period (safety population; 31 May 2019 data cut-off)

Treatment-related TEAE	Ripretinib grade 1/2 (n=85)	Ripretinib grade 3/4/5 (n=85)	Placebo grade 1/2 (n=43)*	Placebo grade 3/4/5 (n=43)*†
Alopecia	42 (49%)	0	1 (2%)	0
Myalgia	23 (27%)	1 (1%)	4 (9%)	0
Nausea	21 (25%)	1 (1%)	1 (2%)	0
Fatigue	20 (24%)	2 (2%)	6 (14%)	1 (2%)
PPES	18 (21%)	0	0	0
Diarrhoea	17 (20%)	1 (1%)	2 (5%)	1 (2%)
Constipation	13 (15%)	0	3 (7%)	0
Weight loss	13 (15%)	0	3 (7%)	0
Decreased appetite	12 (14%)	1 (1%)	2 (5%)	1 (2%)
Blood bilirubin increased	12 (14%)	0	0	0

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Treatment-related TEAE	Ripretinib grade 1/2 (n=85)	Ripretinib grade 3/4/5 (n=85)	Placebo grade 1/2 (n=43)*	Placebo grade 3/4/5 (n=43)*†
Arthralgia	10 (12%)	0	0	0
Muscle spasms	10 (12%)	0	2 (5%)	0

Abbreviations: PPES - Palmar-plantar erythrodysaesthesia syndrome; TEAE - Treatment-emergent adverse event.

* 44 patients were randomised to placebo, but 1 did not receive treatment.

Source: Blay et al, 2020.¹⁵

Treatment-related TEAEs leading to a dose reduction were reported in five (5.9%) of 85 patients in the group who received ripretinib and one (2.3%) of 43 patients who received placebo. Treatment-related TEAEs leading to treatment discontinuation occurred in 4.7% (n = 4/85) of patients who received ripretinib compared to 2.3% (n = 1/43) of patients who received placebo (Table 24).¹⁵

The majority of deaths that occurred during the double-blind phase were due to disease progression. In the ripretinib group, death occurred in 12 out of the 85 patients (14%), of which 11 were due to disease progression and one from an unknown reason.¹⁵ Of the patients in the placebo group, 13 of the 43 (30%) died, of which 11 were due to disease progression and two each separately due to an AE of acute kidney injury and septic shock.¹⁵ One treatment-related death occurred in the ripretinib group due to an unknown cause and one treatment-related death occurred in the placebo group due to septic shock and pulmonary oedema (Table 24).¹⁵

Table 24: Treatment related TEAEs leading to dose modifications (safety population; 31 May 2019 data cut-off)

Categories	Ripretinib (n=85), n (%)	Placebo (n=43)*, n (%)
Any treatment-related TEAE leading to dose reduction¹⁵	5 (5.9%)	1 (2.3%)
Any treatment-related TEAE leading to dose interruption¹⁵	12 (14.1%)	3 (7.0%)

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Any treatment-related TEAE leading to treatment discontinuation¹⁵	4 (4.7%)	1 (2.3%)
Any treatment-related TEAE leading to death¹⁵	1 (1.2%)	1 (2.3%)
Death	1 (1.2%)	0
Pulmonary oedema	0	1 (2.3%)**
Septic shock	0	1 (2.3%)**

*44 patients were randomised to placebo, but 1 did not receive treatment

** Pulmonary oedema and septic shock were reported in the same patient.

Source: Blay et al. 2020,¹⁵

Treatment-related serious adverse events

Treatment-related serious AEs were reported in eight (9%) of 85 patients who received ripretinib (one each of the following: anaemia, cardiac failure, death of unknown cause, dyspnoea, fecaloma, gastro-oesophageal reflux disease, hyperkalaemia, hypophosphataemia, nausea, and upper gastrointestinal haemorrhage; some patients might have experienced more than one event) and three (7%) of 43 patients who received placebo (one each of the following: hyperkalaemia, dehydration, pulmonary oedema, and septic shock; some patients might have experienced more than one event).¹⁵

2.11.2 Pooled adverse reactions data

To perform further safety analyses, the INVICTUS patient population (129 patients diagnosed with advanced GIST who had failed at ≥ 3 prior lines of treatment) was pooled together with those treated in the Phase 1 Study DCC-2618-01-001, in which 277 patients with advanced malignancies were enrolled.^{15,88,89} In the resulting pooled safety population (n=392), the most frequently (>25%) observed adverse reactions in patients who received at least one dose of ripretinib (150 mg) were fatigue (51.0%), alopecia (50.8%), nausea (39.8%), myalgia (37.8%), constipation (37.2%), diarrhoea (32.7%), PPES (29.8%), weight decreased (26.5%) and vomiting (25.8%). The pooled analysis data cut-off is August 2020 (Table 25).⁵¹

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Table 25: Adverse reactions in >10% of patients in the pooled safety group receiving at least one dose of ripretinib

Adverse events	Ripretinib any grade (n=392)
Fatigue	51.0%
Alopecia	50.8%
Nausea	39.8%
Myalgia	37.8%
Constipation	37.2%
Diarrhoea	37.2%
PPES	29.8%
Weight decrease	26.5%
Vomiting	25.8%
Lipase increased	23.7%
Muscle spasms	23.7%
Arthralgia	21.2%
Headache	20.7%
Dyspnoea	20.2%
Hypertension	19.4%
Dry skin	17.6%
Back pain	15.6%
Cough	15.6%
Blood bilirubin increased	14.0%
Oedema peripheral	13.8%
Hypophosphataemia	12.2%
Pain in extremity	12.0%
Pruritis	11.0%
Seborrhoeic keratosis	11.0%

Abbreviations: PPES - Palmar-plantar erythrodysesthesia syndrome.

Source: Deciphera Pharmaceuticals, Summary of Product Characteristics (MHRA), 2023 ²⁴

Grade 3/4 adverse reactions ($\geq 2\%$) observed in patients treated with ripretinib in the pooled safety population (n=392) were lipase increased (14.8%), anaemia (14.0%), abdominal pain (8.2%), hypertension (6.9%), fatigue (4.1%), hypophosphataemia (4.1%), vomiting (2.6%), dyspnoea (2.0%), diarrhoea (2.0%) and blood bilirubin increased (2.0%). Serious adverse reactions ($\geq 1\%$) observed in patients treated with

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ripretinib were anaemia (3.8%), dyspnoea (2.3%), vomiting (2.0%), nausea (1.8%), fatigue (1.5%), blood bilirubin increased (1.3%), constipation (1.0%), and muscular weakness (1.0%).⁵¹

2.11.3 Supportive adverse reactions data: Royal Marsden expanded access program

The toxicity profile observed in the Royal Marsden Hospital expanded access program was in line with available data from INVICTUS, with most toxicities being CTCAE grade (G) 1 or 2.^{15,62} The most common TEAEs reported were fatigue, alopecia, PPES and gastrointestinal and musculoskeletal symptoms (Table 26).⁶⁹

Table 26: TEAEs reported in at least 20% of patients (in the QD group) in the UK expanded access program

Adverse Event	Ripretinib QD any grade (n=45)	Ripretinib QD grade 3+ (n=45)	Ripretinib BID any grade (n=23)	Ripretinib BID grade 3+ (n=23)
Fatigue	35 (77.8%)	0 (0.0%)	18 (78.3%)	0 (0.0%)
Alopecia	21 (46.7%)	0 (0.0%)	9 (39.1%)	0 (0.0%)
Muscle cramp	20 (44.4%)	0 (0.0%)	4 (17.4%)	0 (0.0%)
PPES	17 (37.8%)	1 (2.2%)	9 (39.1%)	0 (0.0%)
Constipation	17 (37.8%)	1 (2.2%)	8 (34.8%)	0 (0.0%)
Arthralgia/myalgia	15 (33.3%)	1 (2.2%)	6 (26.1%)	0 (0.0%)
Weight loss	14 (31.1%)	0 (0.0%)	13 (56.5%)	0 (0.0%)
Diarrhoea	13 (28.9%)	2 (4.4%)	15 (65.2%)	1 (4.4%)
Anorexia	10 (22.2%)	0 (0.0%)	8 (34.8%)	0 (0.0%)

Abbreviations: PPES - Palmar-plantar erythrodysesthesia syndrome.

Source: Lim et al, 2024⁶⁹

During treatment with 150 mg ripretinib QD, ten (22.2%) patients required dose reductions.⁶⁹ Two (4.4%) patients discontinued ripretinib QD due to persistent toxicities despite adequate dose reductions.⁶⁹ After IPDE, 2 (8.7%) patients required dose reductions.⁶⁹ No patient discontinued ripretinib BID due to toxicities. No treatment-related deaths occurred.⁶⁹

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Overall, the expanded access program data did not highlight any new safety signals.

2.12 Ongoing studies

No ongoing studies.

2.13 Interpretation of clinical effectiveness and safety evidence

2.13.1 Principal findings from the clinical evidence

Based on the primary efficacy analysis for the INVICTUS double-blind treatment period, ripretinib led to a statistically significant and clinically meaningful improvement in median PFS compared with placebo (6.3 vs 1.0 months; $p < 0.001$), thereby reducing the risk of disease progression or death by 85% (HR 0.15; 95% confidence interval [95% CI] 0.09 to 0.25).¹⁵ Compared with placebo, ripretinib achieved a clinically meaningful 64% reduction in the risk of death (HR 0.36; 95% CI 0.21 to 0.62), leading to an 8.5-month improvement in median OS vs placebo in the primary analysis (Figure 8, Section 2.6.2).¹⁵ With an additional 19 months follow up, this had increased to a 11.9-month improvement in median OS vs placebo; effectively tripling OS for these patients.^{15,23} At the primary analysis, ripretinib resulted in a clinically meaningful ORR benefit compared with placebo (9% vs 0%).^{15,51} Importantly, ripretinib showed durable, clinically meaningful disease control: 66% of ripretinib-treated patients experienced stable disease for ≥ 6 weeks vs 20% of patients treated with placebo; and 47% vs 5% of patients experienced stable disease for ≥ 12 weeks, respectively.¹⁵ Responses in patients treated with ripretinib were durable, with the median DOR not yet reached at data cut-off (31 May 2019).^{15,51}

In INVICTUS, across all PRO measures assessed, patients treated with ripretinib maintained HRQoL and function for approximately 8 months while it quickly, and significantly, deteriorated for those receiving placebo after just 1 month.¹⁶ Importantly, HRQoL was maintained past the point of median PFS (6.3 months), likely supported by the continued use of ripretinib post-progression in the many patients still receiving clinical benefit.^{16,38} Ripretinib was well-tolerated and demonstrated an acceptable safety profile.⁶² The most common treatment-related TEAEs ($\geq 20\%$) among the 85 GIST patients treated with ripretinib were alopecia (49%), myalgia (28%), nausea

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(26%), fatigue (26%), and PPES (21%). Most of these were grade 1 and 2 in severity.¹⁵ Treatment-related serious adverse events were reported in eight (9%) of 85 patients who received ripretinib and three (7%) of 43 patients who received placebo. Treatment-related TEAEs leading to a dose reduction or treatment discontinuation were reported in 6% (vs 2% in the placebo group) and 5% (vs 2% in the placebo group) of patients receiving ripretinib, respectively.¹⁵

Data from The Royal Marsden Hospital, London, UK, support the generalisability of INVICTUS to clinical practice in the UK.⁶⁹ After a median follow up of 24.2 months (95% CI 19.7–29.7), the median PFS was 7.9 months (95% CI 5.6–19.3) and median OS was 14.0 months (95% CI 9.9–NA), both of which are broadly in line with INVICTUS.^{15,69}

Ripretinib is able to meet a high unmet need in patients with fourth-line advanced GIST by significantly extending PFS and providing durable disease control, thereby preventing the rapid clinical decline otherwise seen in these patients.¹⁵ Consequently, ripretinib allows patients to maintain HRQoL and provides a clinically meaningful survival benefit.^{15,23} During a UK advisory board, clinicians stated that more of their patients would be alive today if ripretinib was a treatment option.¹⁸

2.13.2 Strengths, limitations and generalisability of the clinical evidence

INVICTUS was a double-blind, parallel-group, randomised, placebo-controlled study, which is the gold-standard study design for interventional clinical trials, minimising the risk of confounding factors and allowing direct comparison of the relative efficacy of interventions. Stratification based on key factors such as the number of previous therapies (3 vs ≥ 4) and ECOG performance status (0 vs 1 or 2) ensured that the study accounted for important prognostic factors.

The outcomes measured in INVICTUS were considered clinically and patient relevant by the patient groups Sarcoma UK and GIST Cancer UK. They agreed that OS, PFS, response rate (including partial response rate and DOR), AEs and HRQoL are the most applicable outcomes.^{34,90}

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The results from INVICTUS are relevant to clinical practice in the UK. Ten of 129 patients in INVICTUS were enrolled from two centres in the UK. Overall, the patients included in INVICTUS were representative of patients with advanced GIST in the UK and reflect the known epidemiology of GIST in the UK as reported by Bulusu et al. 2013 and confirmed by clinicians in a UK advisory board.^{18,91} A further 45 patients were treated at the Royal Marsden in London under an expanded access program. The findings from the Royal Marsden retrospective review support the generalisability of INVICTUS to UK clinical practice.

Analyses were limited by the small sample size, from a statistical perspective, which made stratifying patients by more baseline parameters difficult; although, this reflects the rarity of this disease and is aligned with the size of other pivotal trials in this patient population.^{8,92,93}

Although the ripretinib label describes a single daily dose, during INVICTUS, patients were offered the option of escalating to 150 mg BID after disease progression on ripretinib 150 mg QD. This was done on ethical grounds with the intent to provide an additional line of therapy for patients with very late-stage disease.¹⁵ However, across the ITT population more than three-quarters (75.9%) of ripretinib exposure time was on single dose, with only the remaining 24.1% on BID. Although a high proportion (~50%) of patients dose escalated, those patients stayed on BID for a limited time overall. Specifically, only 11 of 43 patients (26%) were treated at this dose for 6 months or longer.⁶⁶ This indicates that the OS benefits seen in INVICTUS are predominantly driven by the single dose rather than BID.

The INVICTUS trial design was, therefore, sufficiently robust to answer the decision problem, in assessing ripretinib vs placebo in patients with advanced GIST in the fourth-line treatment setting.

3 Cost effectiveness

3.1 Published cost-effectiveness studies

A systematic review of the published literature was conducted to identify economic evaluations assessing the treatment of patients diagnosed with advanced/metastatic or unresectable GIST at any line of therapy. Full details of the search are provided in Appendix E.

For extraction, 24 economic evaluation references (n=25 unique CEA [cost-effective analysis]/CUA [cost-utility analysis] studies) were identified. There were 21 CEAs and 3 CUAs that were relevant to the perspective of the UK, Canada, the US, Australia, Spain, the Netherlands, Belgium, Germany, Finland, France, Italy, Poland, Turkey, China, Singapore, Brazil, and Mexico. A summary of economic evaluation studies from a UK NHS perspective is provided in Table 27. A full summary of all the models is provided in the Appendix E.

Table 27: Summary list of published cost-effectiveness studies from a UK NHS perspective

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Pitcher, 2016 ⁹⁴	2016	Model Type: partitioned survival model; Perspective: English NHS; Intervention: Regorafenib + BSC vs BSC	Metastatic/ unresectable GIST (NR)	NR	NR	£35,608 or £40,261 (dependent on crossover adjustment methodology)
Bond, 2009 ⁹⁵	2009	Model Type: Markov model; Perspective: NHS and PSS; Intervention: Sunitinib vs PBO	Unresectable and/or metastatic GIST after failure of imatinib (NR)	NR	NR	Pfizer's base-case analysis £27,365
Hislop, 2011 ⁹⁶	2011	Model Type: Markov model; Perspective: English NHS; Intervention: Imatinib vs BSC	Unresectable and/or metastatic GIST (NR)	NR	NR	ICUR for imatinib 600 mg to sunitinib vs BSC= £71,723 per QALY ICUR for imatinib 800 mg to sunitinib vs BSC= dominated ICUR for imatinib 600 mg to imatinib 800 mg to sunitinib vs BSC= £44,359 per QALY
Wilson, 2005 ⁹⁷		Model Type: state-transition model; Perspective: UK NHS; Intervention: Imatinib vs control	Unresectable and/or metastatic GIST (NR)	NR	NR	£29,789 (range £21,404–33,976)

Abbreviations: BSC - Best supportive care; GIST - Gastrointestinal stromal tumour; ICER - Incremental cost-effectiveness ratio; ICUR - Incremental cost-utility ratio; NR - Not reported; NHS - National Health Service; PBO - Placebo; PSS - Personal Social Services; QALY - Quality-adjusted life year; UK - United Kingdom.

3.2 Economic analysis

This section describes the company's approach to estimating the cost-effectiveness of ripretinib + BSC (ripretinib) vs placebo + BSC (BSC) for patients with advanced GIST who have received prior treatment with three or more kinase inhibitors, including imatinib. Table 28 presents a summary of the economic model. Of the economic analyses identified in the systematic literature review (Appendix E), there was only one that had been conducted of fourth-or-further line ripretinib in patients with advanced GIST.⁹⁸ The model was a Markov structure and was developed from a US perspective. Health state utility values were obtained from the regorafenib pivotal trial in advanced GIST, GRID. The analysis made no attempt to adjust the clinical outcomes for the crossover to ripretinib from the BSC arm in INVICTUS, instead opting to capture the costs of ripretinib in those patients who crossed over from the BSC arm in INVICTUS. Such an approach resulted in a substantial underestimate of the clinical benefits of ripretinib and was therefore not considered appropriate to inform the *de novo* model developed for the present analysis. The primary model used to inform the choice of a PSM structure was the model used for the appraisal of regorafenib for previously-treated unresectable or metastatic GIST, the most recent technology appraisal conducted by NICE for an earlier line of GIST treatment.⁷

Table 28: Summary of the economic model

Aspect	Details	Justification
Patient population	Patients with advanced GIST who have received prior treatment with three or more kinase inhibitors, including imatinib.	Aligned with the ripretinib licence of and final NICE scope.
Analytical method	Partitioned survival model.	The choice of modelling approach was informed by the precedent set by the committee and review group in TA86, TA179 and particularly TA488. ^{5-7,99-101} TA86 and TA179 utilised Markov models with progression-free, progressive disease, and dead states, while TA488 utilised a partitioned survival model with

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Aspect	Details	Justification
		the same health states. The chosen approach is consistent with the method used in most advanced cancer appraisals reviewed by NICE.
Model structure	Three disease-related health states (progression-free, progressed disease, and death), with the progressed disease health state further divided into on-and off-treatment in the ripretinib arm.	A model structure with three disease-related health states is consistent with approaches accepted in previous oncology technology appraisals and utilises the key primary (PFS) and secondary (OS) endpoints from INVICTUS. Further division of the progressed disease state into on-and off-treatment states using a composite endpoint of progression and treatment discontinuation allows the cost, and any ongoing effect, of treatment after progression to be accurately modelled. Four-state partitioned survival models are explicitly documented in NICE DSU TSD 19, in which 5 of the 22 partitioned survival models included in the TA review adopted a four-state approach. ¹⁰²
Discounting options	Costs and health outcomes at 3.5% <i>per annum</i> .	In line with the NICE reference case. ¹⁰³
Perspective	NHS and PSS.	In line with the NICE reference case. ¹⁰³
Treatment arms within executable model	• Ripretinib • BSC	BSC is the established clinical management for 4th line (≥4L) advanced GIST and is therefore aligned with the NICE scope. The choice of ripretinib (ripretinib + BSC) and BSC (placebo + BSC) is also aligned with the treatment arms in INVICTUS.
Clinical efficacy and safety	Data were sourced from: • INVICTUS data • Published clinical evidence • UK general population mortality	INVICTUS is the primary source of evidence of the efficacy and safety of ripretinib in advanced GIST after 3 prior therapies including imatinib.

Abbreviations: BSC – Best supportive care; GIST - gastrointestinal stromal tumours; NHS - National Health Service; NICE - National Institute for Health and Care Excellence; OS – Overall survival; PFS – Progression-free survival; PSS - Personal Social Services; TA - technology appraisal

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3.2.1 Patient population

The population entering the cost-utility model are adult patients with advanced GIST who have received prior treatment with three or more kinase inhibitors including imatinib; this is in line with the scope and decision problem for this evaluation, the UK marketing authorisation and the INVICTUS ITT population.¹⁰⁴ The age at baseline for patients entering the model is 60.1 years and 56.6% of the model baseline population are male, in line with INVICTUS.¹⁵

3.2.2 Model structure

Partitioned survival models (PSMs) have been extensively used to model oncology treatments in the UK healthcare setting. In a review by NICE covering the period May 2013 to February 2016, 22 of 30 (73%) oncology appraisals evaluated by NICE used a PSM.¹⁰²

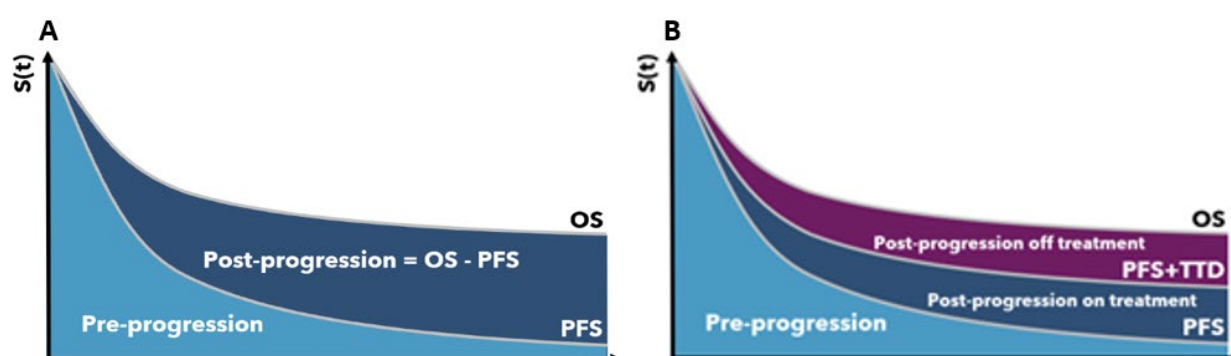
A review of the use of partitioned survival analysis in recent technology appraisals (TAs) of cancer treatments found similar criticisms between the use of PSMs and Markov models. Although Markov models can be more flexible at modelling complex disease trajectories, they have additional data requirements over PSMs. Other model structures have been accepted during health technology assessment (HTA), including time-in-state and cumulative survival models, though these are rarely used.¹⁰²

A PSM structure was selected since it facilitates incorporation of time dependency in the models that govern partition membership over time; in addition, data requirements for partitioned survival analysis were well aligned with and fulfilled by INVICTUS clinical endpoints. A PSM structure is also consistent with previous economic models of GIST such as that used in the appraisal of regorafenib for previously-treated unresectable or metastatic GIST.^{7,101} The model was developed in Microsoft® Excel® for Microsoft 365 MSO (Version 2406; Microsoft Corporation, Redmond, WA). 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 in the ripretinib arm is then further divided into PD on-treatment and PD off-treatment.

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In a typical three-state PSM, the distribution of patients between the PF, PD and dead health states is estimated over time based on survival curves (Figure 22A). The OS and PFS curves are combined to estimate the proportion of patients whose disease has not progressed, who have progressed disease, and who are dead, 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, noting that approximately 80% of patients would be expected to continue ripretinib post-progression in UK clinical practice.³⁸ This phenomenon was captured by dividing the PD state into two sub-states: on treatment and off treatment (Figure 22B).

Figure 22: Overview of partitioned survival model structure derivation



A: Typical three-state PSM structure; **B:** Four-state structure adopted in the current appraisal for the ripretinib arm. Abbreviations: OS - overall survival; PFS - progression-free survival; $S(t)$ - probability of survival at time t .

This approach to capturing post-progression treatment discontinuation was validated by an independent UK health economist with extensive prior experience in health technology assessment in the UK. There is precedent for PSMs that capture additional on- or off-treatment within a disease-related partition (e.g., progression free) both directly in NICE DSU TSD 19 and in five previous technology appraisals included in the review conducted as part of NICE DSU TSD 19.^{102,105-110}

Key features of the economic model and analysis, alongside a comparison with other technology appraisals relating to GIST treatment are presented in Table 29.

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Table 29: Features of the ripretinib economic analysis

	Previous evaluations		Current evaluation	
Factor	TA488 (regorafenib for previously treated unresectable or metastatic GIST)	TA326 (imatinib for the adjuvant treatment of GIST)	Chosen values	Justification
Time horizon	40 years	50 years	40 years	Sufficiently long to capture all lifetime benefits
Treatment waning effect?	No waning implemented	No waning implemented	No waning implemented	No treatment effect waning was modelled due to lack of data
Source of utilities	EQ-5D from trial data	Ara and Brazier (2010), Chabot et al. (2008) and assumptions	EQ-5D-5L data collected from the INVICTUS, mapped onto the EQ-5D-3L using Hernandez Alava et al. (2012)a	EQ-5D-5L data from INVICTUS was mapped to EQ-5D-3L utilities as recommended in the NICE reference case
Source of costs	Bayer, MIMS, NHS reference costs	BNF, NHS reference costs, PSSRU	BNF, NHS reference costs, PSSRU, UK-based published literature	NICE reference case

Abbreviations: BNF - British National Formulary; ERG - Evidence Review Group; EQ-5D-3L - EuroQoL-Five dimensions-Three levels; EQ-5D-5L - EuroQoL-Five dimensions-Five levels; GIST - gastrointestinal stromal tumours; HTA - Health technology assessment; LY - Life year; MIMS - Monthly Index of Medical Specialities; NHS - National Health Service; NICE - National Institute for Health and Care Excellence; OS - Overall survival; PD - progressed disease; PFS - Progression-free survival; PSSRU - Personal Social Services Research Unit; QALY - Quality-adjusted life year; TA - technology appraisal.

3.2.3 Intervention technology and comparators

The intervention technology is ripretinib. As ripretinib is indicated for patients who have received prior treatment with three or more kinase inhibitors, including imatinib, and would represent the last systemic treatment line, the most appropriate comparator was deemed to be BSC.^{18,70} In the model, the base case assumption is that ripretinib would be administered to patients within the licensed indication and at the licensed dose.

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3.3 Clinical parameters and variables

Clinical effectiveness parameters are based on data from INVICTUS.¹⁵ Survival analysis extrapolation was required to inform state occupancy in the model, allowing for evaluation of clinical outcomes over a longer time horizon than that in the trial. From mature OS data for the data cut-off (15 January 2021), 46 patients (54%) in the ripretinib group experienced an OS event (39 [46%] were censored); and 36 patients (82%) patients in the BSC group experienced an OS event (8 [18%] were censored).²³

To validate the applicability of clinical parameters used in the health economic model, clinical experts were consulted during the advisory boards that took place in 2022, 2024 and 2025, details of which are presented in Section 2.3.5.

3.3.1 Progression-free survival

Parametric models were fitted directly to ripretinib + BSC (ripretinib) and placebo + BSC (BSC) patient-level data to provide long-term extrapolations. Crossover of patients from BSC to ripretinib in the INVICTUS was only allowed following disease progression, therefore crossover correction was not required for PFS data. The PFS Kaplan-Meier curves for ripretinib and BSC from the INVICTUS are shown in Figure 5 in Section 2.6.2. Progression was observed within the trial follow-up period for almost all patients in both arms (84% in both, Section 2.6.2, PFS – primary endpoint).²³

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

Inspection of the log-cumulative hazards (Figure 23) and Schoenfeld residual plots (Figure 24) suggest that relative hazards are likely to vary over time; therefore it is not possible to conclude that the PH assumption holds.

Whilst the lines do not intersect on the log-cumulative hazard plot presented in Figure 23, they are not strictly parallel. In addition, the Global Schoenfeld Test shows $p < 0.05$, indicating that the PH assumption does not hold.

Figure 23: PFS survival cumulative log-log plot

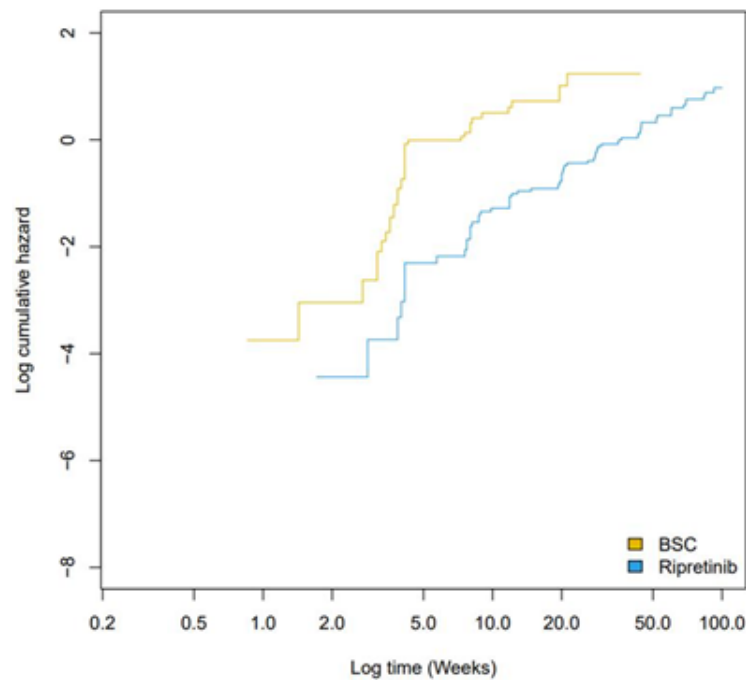
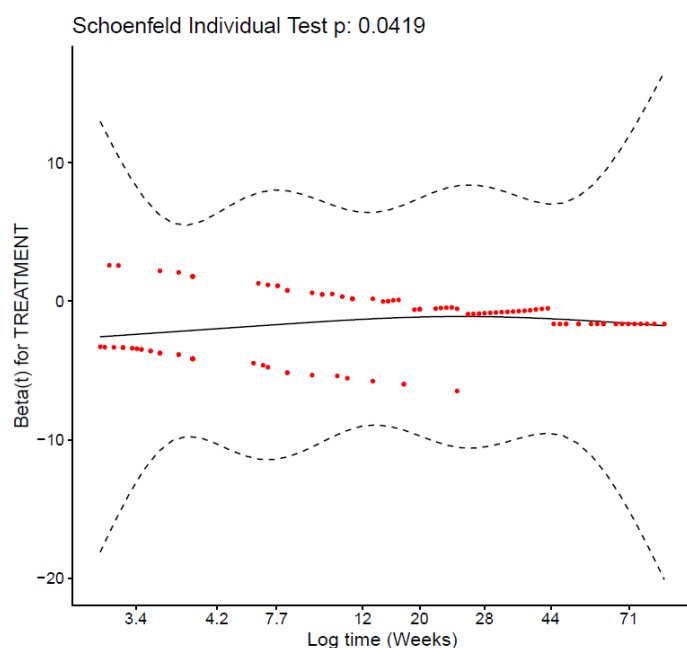


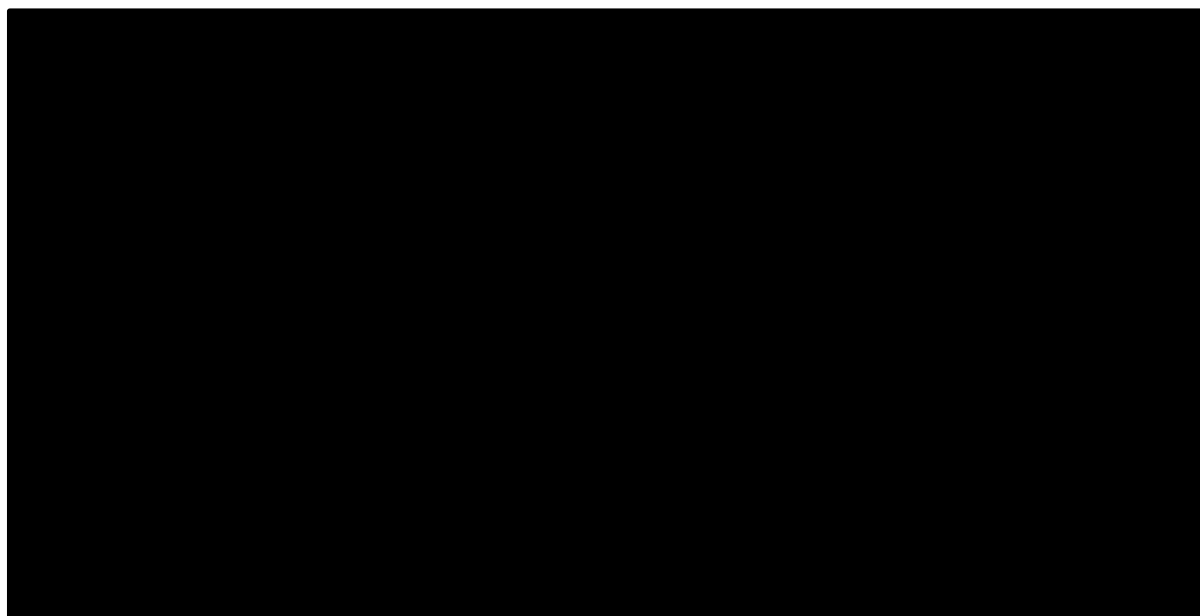
Figure 24: PFS Schoenfeld residuals plot



Abbreviations: Beta(t) - Time-dependent Beta.

Given that Figure 23 and Figure 24 demonstrate that the PH assumption does not hold, and patient-level data were available for both arms, six standard parametric independent models were fitted to each arm of the study data comprising: exponential, Weibull, Gompertz, log-logistic, log-normal and the generalised gamma (Figure 25). A summary of the goodness-of-fit statistics for the PFS extrapolations is presented in Table 30 (base case in bold). More complex models, such as piecewise spline-based models, mixture models, flexible proportional-hazards models, or proportional-odds models, were not considered as the independent parametric models appeared to be suitable for modelling PFS based on inspection of log-cumulative hazards, visual goodness-of-fit and plausibility of the extrapolated portion of the curves.¹¹¹

Figure 25: PFS independent parametric curves for ripretinib and BSC



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

Table 30: AIC and BIC statistical goodness-of-fit data for PFS

Distribution	Ripretinib		BSC		Combined	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	460.51	462.95	127.72	129.50	588.23	592.45
Weibull	461.10	465.98	127.71	131.28	588.81	597.26
Gompertz	462.47	467.36	128.99	132.55	591.46	599.91
Log-logistic	459.57	464.46	109.61	113.17	569.18	577.63
Log-normal	457.14	462.03	112.57	116.13	569.71	578.16
Generalised gamma	458.75	466.08	112.01	117.37	570.77	583.45

Bold denotes base case survival distribution.

Abbreviations: AIC - Akaike information criterion; BIC - Bayesian information criterion; BSC - Best supportive care; PFS – Progression-free survival.

The independent parametric curves 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.¹¹¹ This allows the two-dimensional treatment effect in the shape and

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scale parameters to differ between treatment arms but prevents the survival hazards from being significantly different between arms. The combined Akaike information criteria (AICs) were calculated but were too close to be used to make a judgement on the best statistical fit. The log-normal distribution was ultimately selected as the base-case curve used for PFS extrapolation for both treatment arms, based on having: the best AIC and BIC fit to ripretinib arm data; among the lowest combined AICs and BICs across treatment arms; and good visual fit. The log-normal distribution also provides a more conservative long-term estimate of the proportion of patients free of progression than the log-logistic distribution (e.g., █ progression free after 3 years with the log-normal distribution versus █ with the log-logistic distribution in the ripretinib arm). Conversely, the log-normal distribution shows fractionally better outcomes in the BSC arm, with █ of patients progression free after 6 months versus █ with the log-logistic distribution.

3.3.2 Overall survival

In INVICTUS, patients who were randomly assigned to BSC were given the option to crossover to receive open-label ripretinib.

As the true survival associated with BSC will be confounded, conventional survival analysis is likely to underestimate the survival benefit associated with ripretinib. Due to the high proportion of patients who crossed over (30 of 44 patients [68%] at data cut-off of 15 January 2021), using the results of the ITT analysis for OS in the model was deemed inappropriate.

Treatment crossover in INVICTUS occurred following disease progression and was therefore non-random. The NICE Decision Support Unit (DSU) recommends implementation of a variety of potentially appropriate crossover- adjustment approaches when adjusting for a high degree of crossover. Such approaches take into account trial characteristics, the switching mechanism, the treatment effect, and data availability.¹¹² The methods recommended by the DSU include: the Inverse Probability of Censoring Weights (IPCW) method, the Rank Preserving Structural Failure Time (RPSFT) model, and the two-stage approach.¹¹²

Overall survival adjustment for crossover

Crossover adjustment: Inverse probability of censoring weights

The IPCW method was considered but not used due to the small sample size from a statistical perspective and the high proportion of BSC patients crossing over to ripretinib treatment (only 14 patients in the BSC arm did not enter the open-label period); these factors can be responsible for introducing high levels of error in treatment effect estimates and both may introduce uncertainty into the IPCW analysis.¹¹²

Crossover adjustment: Rank preserving structural failure time

The RPSFTM method uses a g-estimation procedure to determine treatment effect, ψ .¹¹³ The treatment effect is estimated by balancing counterfactual event times (that is, the time that would have been observed if no treatment were received in either randomised group) across randomised groups. A key advantage of the RPSFTM method is that it is randomisation-based and requires only the randomised treatment groups, observed event times, and treatment history in order to estimate counterfactual survival times.¹¹³ The method relies on the assumption that a 'common treatment effect' exists and so the treatment effect for switchers must be the same (relative to the time taking treatment) as that for those initially randomised to the experimental treatment.

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 were the log-rank and the Wald test from a Cox or Weibull regression model. All three options were explored to derive the acceleration factor ($\exp(\psi_0)$) and time ratio ($\exp(-\psi_0)$) associated with ripretinib treatment in the ITT population. The log-rank, Cox and Weibull models all gave output time ratios of >15 (Table 31). When considering the counterfactual survival times in Figure 26, the dissimilarity between curves indicates that the g-estimation did not produce a robust outcome. Figure 26 shows the log-rank option but the Cox and Weibull options produced very similar

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results. As patients were only allowed treatment switch following disease progression, it was considered unlikely that the ‘common treatment effect’ assumption would hold. As such, the RPSFTM method was ruled out for the base case, but was explored in scenario analyses.

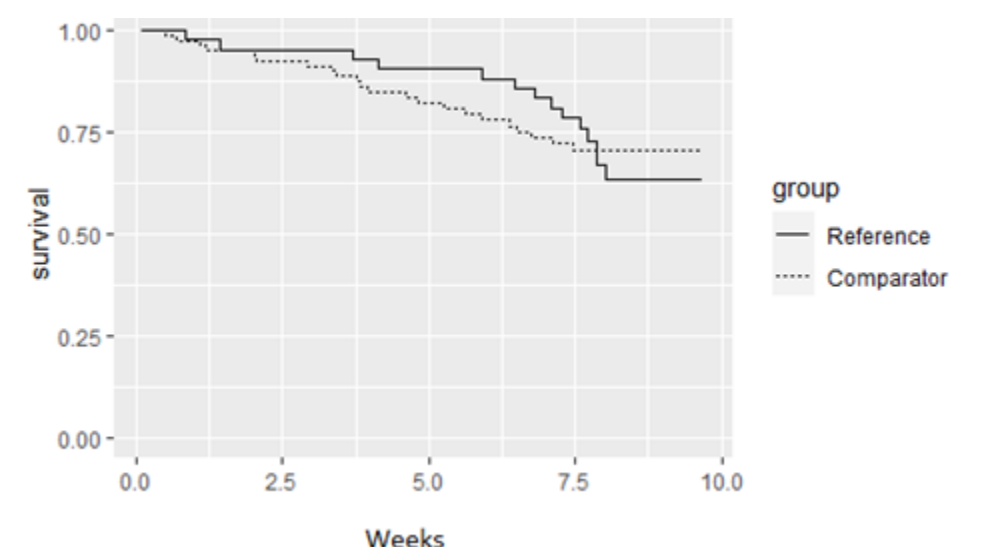
The ‘RPSFTM’ package allows for deviations from the common treatment effect to be modelled through use of a treatment-effect modifier variable, k_i , which modifies the counter-factual treatment-free event times by multiplying the treatment effect by k_i . While such modification is likely to result in an RPSFT model that is biased (in the absence of further adjustments for heterogeneity in the underlying characteristics that may drive differences in treatment effect), this option was explored. In the absence of data to inform the value of k_i , analyses were run in which k_i values were set to 1 (common treatment effect; no deviation) and 0.5 (treatment effect half as strong). With k_i set to 0.5, the acceleration factor $\exp(\psi_0)$ changed from 0.06 to 0.07. Given the likelihood that such an RPSFT model would be biased and that the choice of treatment-effect modifier variable was arbitrary (in the absence of observed data), these analyses were not used in the base analysis, but were explored in a scenario analysis in which the best-fitting distribution to the RPSFT model with k_i set to 0.5 (Weibull distribution; AIC: 292.7, BIC: 296.3) was used as the basis of modelling OS in the BSC arm. An additional scenario analysis was then conducted maintaining the log-logistic distribution adopted in the base case analysis (which used the simple two-stage adjustment model).

Table 31: Rank preserving structural failure time model output

Output	Log-rank	Cox model	Weibull model
Psi (95% CI)	-2.75 (NA, -1.50)	-2.75 (NA, -1.49)	-2.75 (-1.50, NA)
Exp (psi)	0.06	0.06	0.06
Exp (-psi)	15.57	15.57	15.57

Abbreviations: CI - Confidence Interval; NA - Not Available

Figure 26: Counterfactual event times by treatment arm, presented as a Kaplan-Meier plot of transformed treatment-free time



Reference represents RPSFT-adjusted (i.e. counterfactual) placebo arm. Comparator represents RPSFT-adjusted (i.e. counterfactual) ripretinib arm.

Crossover adjustment: Two-stage approach

The two-stage approach to crossover adjustment was considered and relies on the following assumptions:¹¹²

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

Two models were explored, one included time to progression as a co-variate (simple model) and the other included time to progression, Eastern Cooperative Oncology Group performance status (ECOG), QoL (quality of life) and age as co-variables (complex model). The following assumptions were made:

- 7 of 44 patients in the BSC group had progression censored but continued to be followed up. To avoid reducing an already small sample size, it was assumed that censored time to progression values equate to documented time to progression for these patients

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- ECOG PS and QoL values recorded at the closest time to progression were used in the analysis.

As time to progression was the only statistically significant co-variate, the use of co-variables in the complex model would add additional uncertainty to the analysis; given the small sample size, the simple model was used in the base-case analysis, while the complex model was explored in scenario analyses.

The resulting time ratio was then used to ‘shrink’ the post-progression survival times for switching patients to derive a counterfactual dataset unaffected by switching. The base-case analysis was performed with recensoring to guard against informative censoring.¹¹⁴ The resulting median OS times for the base-case analysis (simple model) and complex model are presented in Table 32. The adjusted OS BSC base-case Kaplan-Meier curve is shown in Figure 27.

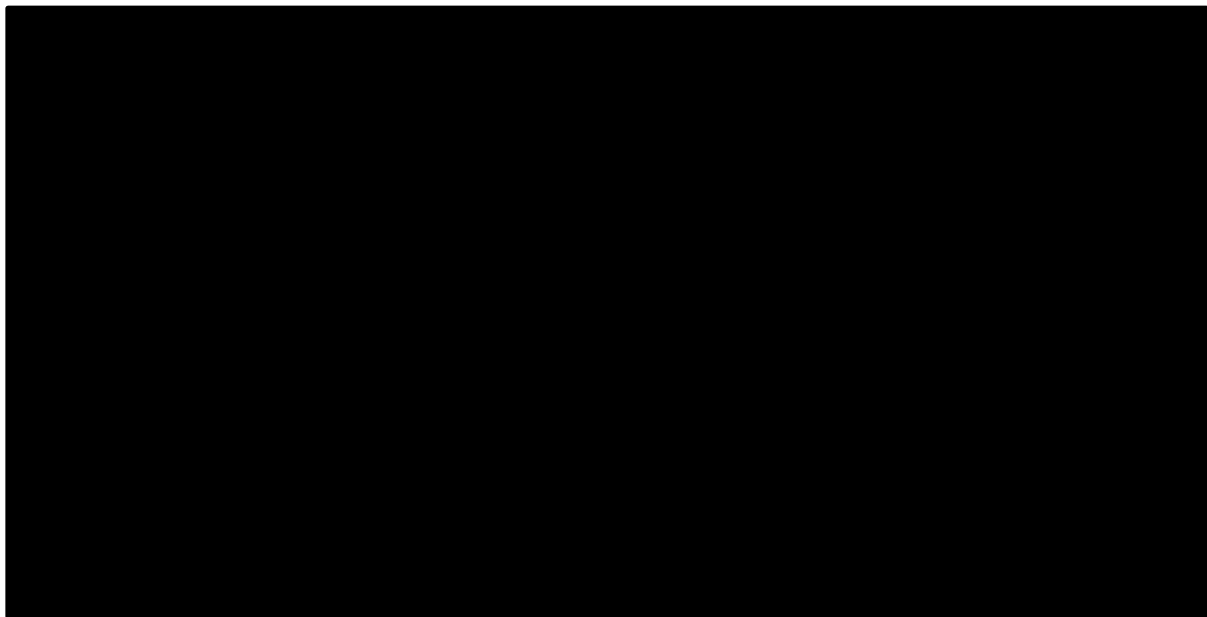
Table 32: Median OS with BSC

Crossover adjustment method	Median OS with BSC (weeks)
Unadjusted	27.43
Two-stage adjustment simple model (treatment switch, time to progression as co-variables; base case)	■
Two-stage adjustment complex model (treatment switch, time to progression, ECOG PS, age and QoL as co-variables)	■

Bold denotes base case approach.

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

Figure 27: Kaplan-Meier curve adjusted OS for BSC



Abbreviations: BSC - Best supportive care; OS - Overall survival.

The two-stage approach was ultimately chosen as the most robust estimate as switching in INVICTUS occurred only after a well-defined clinical event (giving a good basis for the 'secondary baseline' required in two-stage estimation). The two-stage approach also does not rely on the common treatment effect assumption, nor is it as adversely affected by a high proportion of patients undergoing crossover as the IPCW approach.

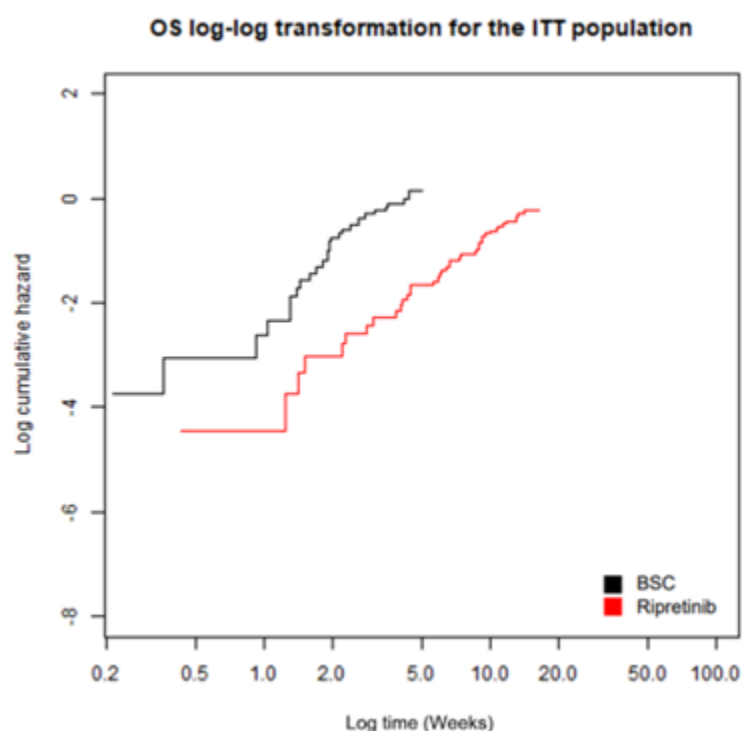
The two-stage estimate was further validated by a UK clinician advisory board, where it was unanimously agreed that an adjusted median OS of 11.2 weeks for patients receiving BSC is clinically plausible.³⁸ This reflects clinical practice where patients receiving BSC after exhausting all active treatment options usually survive for 2 to 3 months.³⁸

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

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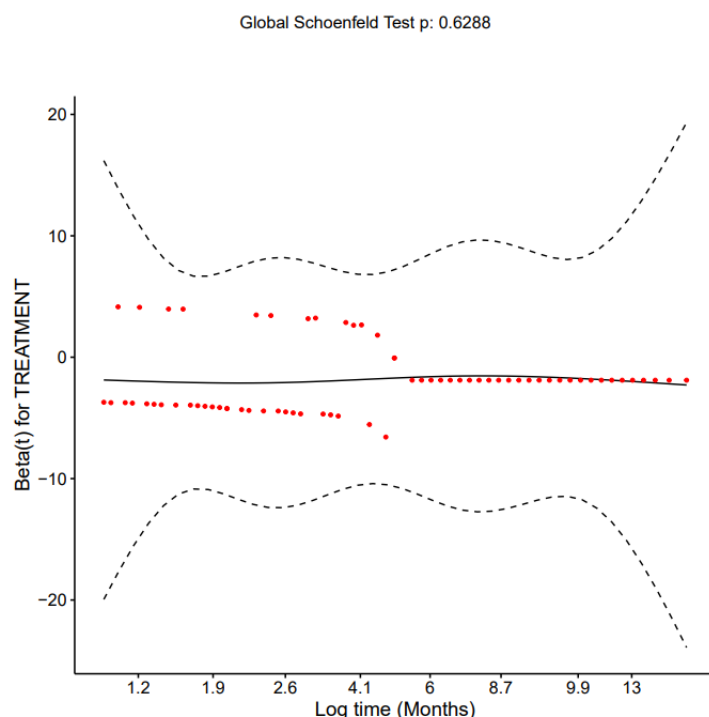
Inspection of the log-cumulative hazards (Figure 28) and Schoenfeld residual plot (Figure 29) suggests that it would be reasonable to accept the PH assumption.

Figure 28: Overall survival cumulative log-log plot



Abbreviations: BSC - Best supportive care.

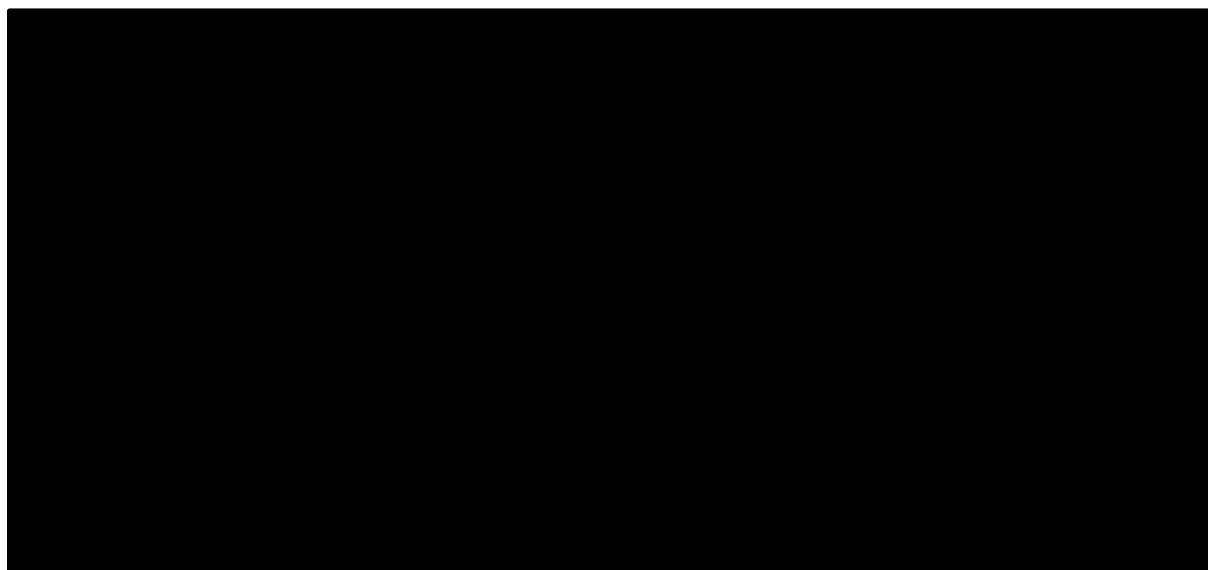
Figure 29: Overall survival Schoenfeld residual plot



Abbreviations: Beta(t) - Time-dependent beta.

While log-cumulative hazard curves do not intersect on the hazard plot presented in Figure 28, the lines are not strictly parallel. The Global Schoenfeld Test gave a p-value of $p > 0.05$, indicating that it was not possible to rule out proportional hazards.¹¹⁵ However, standard parametric independent models (exponential, Weibull, Gompertz, log-logistic, log-normal and the generalised gamma) were ultimately fitted to each arm on the grounds that separate models require fewer assumptions, provide greater flexibility in modelling survival curves, and can provide more accurate survival estimates particularly in the extrapolated portion of the curves. Dependent models necessitate the behaviour of the model tails to be shared between arms and mask any subtle departures from the proportional hazards assumption (Figure 30). A summary of the goodness-of-fit statistics for OS extrapolations is presented in Table 33.

Figure 30: Overall survival independent parametric curves for ripretinib and BSC



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

Table 33: AIC and BIC statistical goodness-of-fit for OS data

Distribution	Ripretinib		BSC (simple 2SRC)		Combined	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	415.08	417.52	137.48	139.26	552.55	556.78
Weibull	416.92	421.81	134.72	138.29	551.64	560.10
Gompertz	416.66	421.54	137.24	140.81	553.90	562.35
Log-logistic	414.15	419.04	133.23	136.80	547.38	555.83
Log-normal	414.14	419.03	134.49	138.06	548.63	557.09
Generalised gamma	416.10	423.43	135.89	141.25	551.99	564.67

Bold denotes base case survival distribution.

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

Independent parametric curves fitted the data and produced good visual predictions for ripretinib and BSC within the observed period. Combined AICs and BICs were calculated across treatment arms, yielding total values that were very closely matched among the best performing models and did not therefore meaningfully differentiate

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between the models in terms of statistical fit; the log-logistic model had the lowest combined AIC at 547.38 but this was only 1.25 lower than the log-normal. Beyond the goodness-of-fit statistics, the log-logistic model extrapolation predicts that 8.6% of patients in the ripretinib arm would be alive at 10 years, which is in line with the upper end of estimates stated at a clinical advisory board held in July 2024. Clinical advisors generally agreed that the shape of the log-logistic empirical hazard function would likely be most reflective of clinical reality. The clinical plausibility and validity of 8.6% of patients being alive at 10 years is also supported by 10-year survival rates for patients who initiated first and second lines of therapy (10-23%).^{46,77,116} After progressing on imatinib, patients usually progress quickly with sunitinib and regorafenib treatment, with each line of therapy providing only 6 to 9 months of benefit before the disease progresses.^{8,116} If the survival rate of patients treated with sunitinib at 2L is 10% at 10 years, 10% survival at 9 years with ripretinib (as modelled in the base case) is plausible.

In addition to parametric models of OS based on INVICTUS data, the model estimates general population mortality to ensure that survival in the fourth-line GIST population does not exceed that in the general population. General population mortality rates were estimated based on life tables published by the Office of National Statistics.¹¹⁷ Age-dependent background mortality is applied to the OS partition to ensure that survival does not exceed survival for the general population.

Overall survival adjustment for IPDE

Adjustment for post-progression IPDE was attempted using various methodologies (Section 2.6). However, given the considerable uncertainty surrounding the appropriate methodology, the heterogeneity in outcomes from the different approaches employed, and clinician uncertainty surrounding the magnitude of the effect of IPDE on survival, these approaches were not used in the base case but were assessed as scenario analyses.

Censored BID-dosing analysis

Two analyses were conducted in which parametric models were derived using data from patients in the ripretinib arm of INVICTUS who had:

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- Progressed disease and had escalated dose to ripretinib 150 mg BID, in combination with those whose disease had not progressed
- Progressed disease and had not escalated to ripretinib 150 mg BID, in combination with those whose disease had not progressed.

Parametric models of OS (based on the exponential, gamma, Gompertz, log-logistic, log-normal, and Weibull distributions) were fitted to each of these subgroups to establish the bounds. The goodness of fit of the models was assessed using AIC and BIC (Table 34), with the exponential model being the best fit for the ‘plus IPDE progressors’ subgroup, and the log-normal model being the best fit for ‘plus QD progressors’ subgroup.

Table 34: Goodness-of-fit of parametric OS models to subgroups by IPDE status

Population	Distribution	AIC	BIC
Non-progressors + IPDE progressors	Exponential	293.8	295.9
	Generalised gamma	295.5	299.7
	Gompertz	295.7	299.9
	Log-logistic	294.1	298.3
	Log-normal	294.9	299.1
	Weibull	295.7	299.9
Non-progressors + QD progressors	Exponential	189.8	191.5
	Generalised gamma	191.3	194.7
	Gompertz	188.1	191.5
	Log-logistic	188.7	192.1
	Log-normal	188.0	191.5
	Weibull	190.9	194.3

Bold denotes best model by statistical fit.

Abbreviations: AIC - Akaike information criterion; BIC - Bayesian information criterion; IPDE - Inpatient dose escalation; QD - Quaque die (every day or once daily).

Cox proportional hazards time-varying analysis for IPDE

The time-varying Cox proportional hazards regression IPDE adjustment models (Section 2.6) were incorporated into the model by way of a weighted average hazard

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adjustment to the ripretinib OS parametric model (with hazard ratios weighted by the proportion in the on-treatment PD partition which is in turn dictated by the selected OS curve and PFS+TTD curve). Three models were developed with different covariate adjustments: one model with study treatment as a covariate; one model with study treatment, progression, ECOG, EQ-5D VAS, lesion diameter sum and lesion diameter change from baseline as covariates; and one model with study treatment, progression status, ECOG, EQ-5D VAS, lesion diameter sum, lesion diameter change from baseline, baseline lesion diameter sum, age, sex, race, region, baseline BMI, hepatic impairment, number of prior therapies, baseline creatinine clearance (CrCl), and baseline renal impairment as covariates (Table 35). The study treatment-only model (HR=1.58) and the complex model with all covariates (HR=1.37) were used as the basis of scenario analyses.

Table 35: Time-varying Cox proportional hazard regression adjustment outcomes

Covariates	Hazard ratio (95% CI)	P-value
Study treatment	1.58 (0.85, 2.95)	0.150
Study treatment, progression, ECOG, EQ-5D VAS, lesion diameter sum, lesion diameter (% change from baseline)	1.43 (0.66, 3.12)	0.365
Study treatment, progression, ECOG, EQ-5D VAS, lesion diameter sum, lesion diameter (% change from baseline), baseline lesion diameter sum, age, sex, race, region, baseline BMI, hepatic impairment, number of prior therapies, baseline CrCl, and baseline renal impairment	1.37 (0.66, 2.84)	0.397

Note: Hazard ratios >1 indicate higher mortality hazard with ripretinib BID versus QD.

Abbreviations: BMI - body mass index; CI, confidence interval; CrCl - creatinine clearance; ECOG - Eastern Cooperative Oncology Group; EQ-5D, EuroQol 5D; VAS – visual analog scale.

Two-stage adjustment for IPDE

The two-stage adjustment approach (Section 2.6) was used to capture the effect of IPDE on OS via a series of survival time ratios based on two possible covariate adjustment models: simple (accounting only for time to progression) and complex Company evidence submission template for ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments (review of TA881) [ID6496]

(accounting for time to progression [days], ECOG performance status at progression, EQ-5D VAS score at progression, and age at baseline [years]). The exponential, Weibull, log-normal, log-logistic, and generalised gamma distributions were then used to model survival time ratio with each of the two covariate adjustment approaches, with the time ratio estimates presented in Table 36. These time ratio adjustments were incorporated into the model in scenario analyses by way of weighted average hazard adjustments to the OS parametric model (with time ratios treated equivalently to inverse hazard ratios, but weighted by the proportion in the on-treatment PD partition); the analysis was therefore equivalent (in terms of OS) to all patients in the on-treatment PD partition escalating to BID.

Table 36: Survival time ratio estimates and AIC goodness-of-fit measures for a two-stage adjustment to account for the effect of IPDE on OS

Covariate adjustment approach	Distribution	AIC	Survival time ratio estimate (95% CI)
Simple	Exponential	166.53	2.44 (1.19, 5.01)
	Weibull	167.78	2.68 (1.16, 6.15)
	Log-normal	159.96	3.45 (1.56, 7.60)
	Log-logistic	160.26	4.28 (1.90, 9.64)
	Generalised gamma	160.9	3.21 (1.48, 6.97)
Complex	Exponential	158.7	1.95 (0.72, 5.25)
	Weibull	160.7	1.94 (0.71, 5.34)
	Log-normal	149.51	2.40 (1.10, 5.25)
	Log-logistic	150.5	2.34 (1.03, 5.29)
	Generalised gamma	144.51	2.72 (1.57, 4.74)

Notes: Survival time ratios >1 indicate longer survival with ripretinib BID versus QD. Bold denotes best model by statistical fit.

Abbreviations: AIC - Akaike information criterion; CI - Confidence interval; IPDE - Inpatient dose escalation; OS – Overall survival.

3.3.3 Time to treatment discontinuation (TTD)

Post-progression ripretinib use was captured in the ripretinib arm of the model through division of the PD state into two substates: on treatment and off treatment.

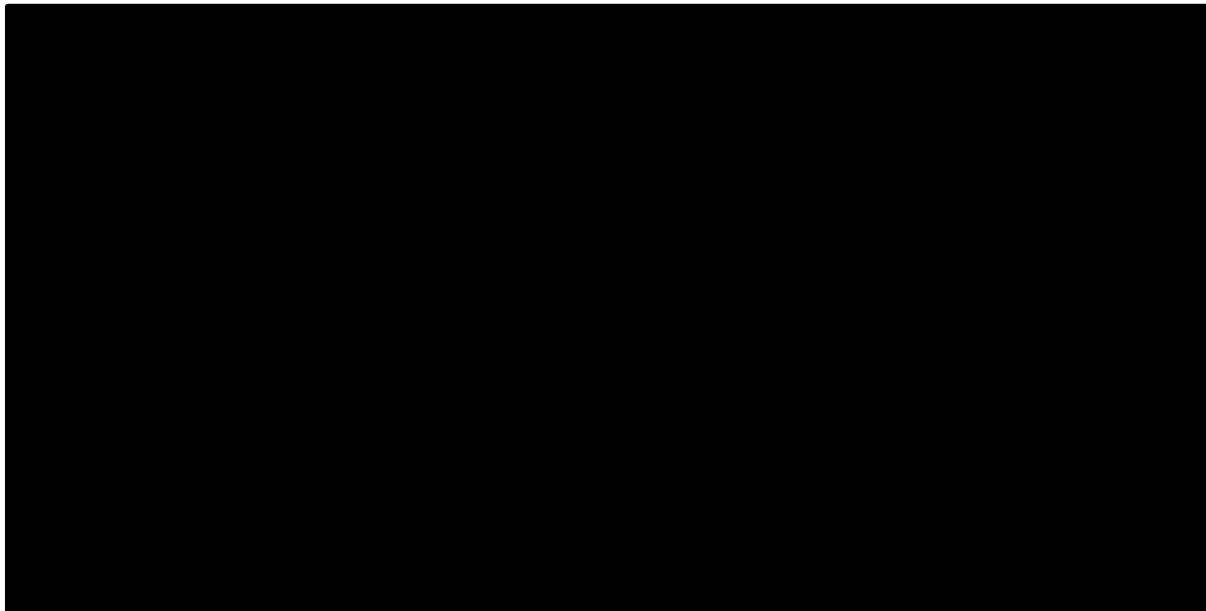
The parametric survival models used to divide the PD state into on treatment and off treatment were based on an analysis of a composite endpoint of PFS and treatment

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discontinuation, defined as follows: the time from study start to a composite endpoint of PFS plus treatment discontinuation (either QD or BD) over the double-blind and open-label periods was derived. Event time was measured from the date of randomisation to the latest of PFS or treatment discontinuation. Patients without either event were considered censored and censoring time was measured from the date of randomisation to the latest of the two component times (PFS, last treatment), regardless of event/censoring for each component. Due to PFS censoring rules pertaining to two or more missing assessments (in line with the INVICTUS SAP 8.1), patients who did not either discontinue treatment and/or were considered censored for PFS, and who died were assumed to have the composite endpoint event at the time of their death. The analysis was restricted to ITT patients who were randomly assigned to ripretinib.

The Kaplan-Meier curves of this composite endpoint are presented alongside the OS and PFS endpoints in Figure 31.

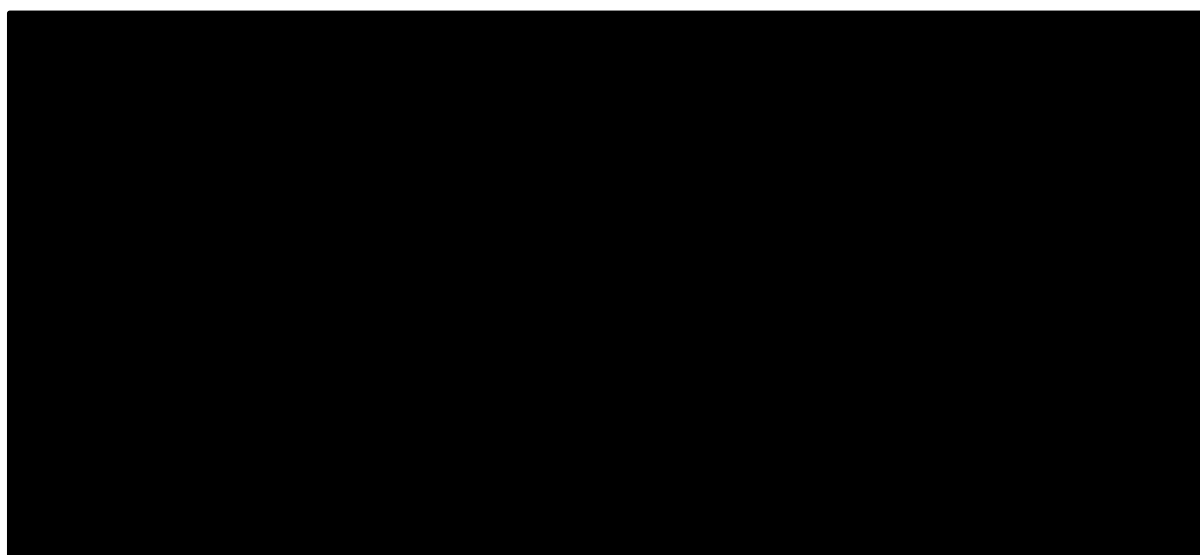
Figure 31: Kaplan Meier curves of the composite endpoint of PFS and treatment discontinuation (green) alongside the Kaplan Meier curves for OS (blue) and PFS (red)



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

Eight standard parametric independent models were fitted to ripretinib arm data comprising: exponential, Weibull, Gompertz, log-logistic, log-normal, gamma, generalised gamma, and generalised F (Figure 32). A summary of goodness-of-fit statistics for the composite PFS and treatment discontinuation endpoint extrapolations is presented in Table 37. The empirical hazard functions of the parametric models fell into one of three groups: monotonically increasing (gamma and Weibull), near-linear (exponential and Gompertz), and non-monotonic unimodal functions (log-normal, log-logistic, generalised gamma, and generalised F) (Appendix J).

Figure 32: Time to the composite of PFS and discontinuation of ripretinib (any dose)



Abbreviations: AIC - Akaike information criterion; BIC - Bayesian information criterion.

Table 37: AIC and BIC statistical goodness-of-fit data for composite of PFS and discontinuation of ripretinib (any dose)

Distribution	Ripretinib	
	AIC	BIC
Exponential	552.2	554.7
Weibull	553.1	558.0
Gompertz	554.2	559.1
Log-logistic	549.5	554.3

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Log-normal	552.5	557.4
Gamma	552.3	557.2
Generalised gamma	552.4	559.7
Generalised F	551.8	561.6

Bold denotes base case survival distribution.

Abbreviations: AIC - Akaike information criterion; BIC - Bayesian information criterion.

When selecting a model for the base case, there is little to differentiate between the goodness-of-fit criteria from all models tested (AIC: 549.5–554.2 and BIC: 554.3–559.7). During a UK advisory board clinicians were asked to consider the most appropriate model for the base case, based on the shape of the empirical hazard functions. Clinicians agreed that the most appropriate curve for TTD was exponential and so this was chosen as the base case model (see empirical hazards plot for composite endpoint in Appendix C).¹⁸ Furthermore, they deemed the time-on-treatment trajectory for the exponential model to be clinically plausible, with a small proportion patients remaining on ripretinib at 3 [REDACTED] and 5 [REDACTED] years being a reasonable assumption. This aligns with experience with patients treated with ripretinib in clinical practice (at the Royal Marsden through INVICTUS and the expanded use program).³⁸

3.3.4 Subsequent treatments and drug exposure

As ripretinib is anticipated to be the last line of therapy for GIST in UK clinical practice, no subsequent treatments were modelled in the ripretinib arm with patients incurring only the costs of BSC after treatment discontinuation. A compliance rate and relative dose intensity of 100% and 96.5% respectively were used in the base case analysis, with the latter derived from the double-blind period of INVICTUS.¹⁵

3.4 Measurement and valuation of health effects

3.4.1 Health-related quality-of-life data from clinical trials

EQ-5D-5L assessment was a pre-specified secondary endpoint in INVICTUS. EQ-5D-5L assessments were completed using an electronic PRO (ePRO) system 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). Patients were asked to rate their health on that specific day using a vertical visual analogue scale. The five questions were scored and together contributed to the EQ-5D-5L index (utility) score of between 0 and 1 (1 being perfect health) and was calculated using the developers' algorithm based on country-specific reference score sets (Van Hout et al., 2012).¹¹⁹ An ANCOVA model with stratification factors as factors will be used to compare change from baseline to Day 1 of Cycle 2 between the two treatment arms. A summary of EQ-5D-5L index (utility) scores is shown in Table 38.

These methods align with the NICE reference case. Although the values were not generated solely from a UK population, data from the Royal Marsden expanded use program demonstrates the generalisability of INVICTUS to UK patients with advanced GIST; this was also validated by clinicians.^{38,69} INVICTUS is the most appropriate and robust data for modelling given that it is sourced from the pivotal Phase 3 trial for ripretinib in the population relevant to the NICE decision problem. No other clinical trials have collected such data to our knowledge.

Table 38: Summary of EQ-5D-5L index (utility) scores derived from INVICTUS (31 May 2019 data cut-off)

	Placebo	Ripretinib
Baseline		
N	42	74
Mean (SD)	0.7547 (0.25210)	0.7696 (0.2846)
Cycle 2, day 1		
N	33	78
Mean (SD)	0.7545 (0.22010)	0.7762 (0.16802)
Change from baseline		
N	32	70
Mean (SD)	-0.0596 (0.19535)	-0.0058 (0.13986)
Adjusted mean (SE) ^a	-0.0606 (0.02796)	-0.0094 (0.01957)
Difference in adjusted mean (95% CI) ^b	0.05 (-0.02 to 0.12)	
P value ^c	0.133	

^aP value from Cochran-Mantel-Haenszel test; ^bDifference of placebo arm – ripretinib arm; ^cEstimated from an ANCOVA model that included factors for study treatment, number of prior anticancer treatment, and ECOG status at baseline as fixed effects. Analysis not adjusted for multiplicity.

Abbreviations: CI - Confidence interval; SD - Standard deviation; SE - S, standard error.

3.4.2 Mapping

As EQ-5D-5L data were collected directly in INVICTUS, completed EQ-5D-5L questionnaires were mapped to EQ-5D-3L UK utilities as described by Hernandez-Alava and Pudney (2022).¹²⁰

3.4.3 Health-related quality-of-life studies

Appendix F documents the methodology and findings of systematic searches for relevant health-related quality-of-life data. Table 39 presents the results of the studies identified in the literature review.

Table 39: Utility values associated with specific disease states for advanced/metastatic or unresectable GIST

Reference	Population	PF utility point estimate	PD utility point estimate	Method of elicitation/valuation
First-line GIST				
Wilson et al. (2005) ⁹⁷	Unresectable and/or metastatic GIST (1L)	0.935	0.875	ECOG category mapped to EQ-5D
Banerjee et al. (2020) ¹²¹	Metastatic GIST (1L & 2L)	-	0.935 ^d 0.577 ^b	Measured EQ-5D
Second-line GIST				
NICE (sunitinib) (2009) ⁶	Unresectable and/or metastatic malignant GIST after failure of imatinib mesylate treatment due to resistance or intolerance	0.731 ^a 0.781 ^b	0.577	Measured EQ-5D
Paz-Ares et al. (2008) ¹²²	Imatinib-resistant or intolerant metastatic and/or unresectable GIST	0.712 ^a 0.781 ^b	0.577	Measured EQ-5D
Chabot et al. (2008) ¹²³	GIST intolerant or resistant to imatinib	0.712 ^a 0.781 ^b	0.577	Measured EQ-5D
Hislop et al. (2011) ⁹⁶	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) ⁹⁶	Unresectable and/or metastatic GIST whose disease had progressed on 400 mg/day	0.935 ^a	-	Measured EQ-5D
Third-line GIST				
Regorafenib PSD (GRID trial) (2015)	GIST patients who must have previously failed or be intolerant to imatinib mesylate and sunitinib, must have a WHO performance status of 0	0.767	0.647	Measured EQ-5D

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Reference	Population	PF utility point estimate	PD utility point estimate	Method of elicitation/valuation
	or 1, and must be aged 18 years or older			
SMC (regorafenib) ¹²⁴	Unresectable or metastatic GIST who progressed on or are intolerant to prior treatment with imatinib and sunitinib	0.74	0.68	Measured EQ-5D
Zolic et al. (2015) ¹²⁵	Metastatic and/or unresectable GIST (3L)	0.872	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) ¹²⁵	Metastatic and/or unresectable GIST (3L)	0.850	0.814	Simplest repeated measures model, not including variables for treatment effect
Poole et al. (2015) ⁴¹	Advanced GIST (3L)	0.760 ^c 0.767 ^d	0.647	Measured EQ-5D
Liao et al. (2021) ⁹⁸	Advanced GIST (3L)	0.767	0.647	Measured EQ-5D
Rui et al. (2021) ¹²⁶	Advanced GIST (3L)	0.780 ^e 0.779 ^f	0.647	Measured EQ-5D
Zhang et al. (2023) ¹²⁷	Recurrent/metastatic GIST (3L+)	0.800	0.700	Measured EQ-5D
Fourth-line GIST				
Jones et al. (2022) ⁶⁰	Advanced GIST with progression-free state in 4L+ treated with ripretinib	0.810	0.670	Measured EQ-5D

^aSunitinib ^bPlacebo + BSC ^cBaseline ^dOn treatment ^ePazopanib ^fRegorafenib

Abbreviations: 1L - First-line; 3L - Third-line; EQ-5D - EuroQoL-Five Dimensions; GIST - Gastrointestinal stromal tumour; PSD - Public summary document; SMC - Scottish Medicines Consortium; WHO - World Health Organisation.

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3.4.4 Adverse reactions

Ripretinib was well-tolerated and associated with an acceptable safety profile in INVICTUS. The overall frequency of TEAEs was similar between the ripretinib and BSC groups (99% vs 98%).⁶² Safety findings for the January 2021 data cut were consistent with the previous primary analysis results.²³

Approximately half of patients in the ripretinib group experienced a grade 3 or 4 TEAE (49%) with 8% experiencing a TEAE leading to treatment discontinuation.²³ Grade 3 or 4 TEAEs and TEAEs leading to discontinuation were reported in a similar proportion of patients in the BSC group (44% and 12%, respectively). Table 40 details grade 3 or 4 TEAEs that occurred in ≥5% of patients in either treatment arm that were included in the model.²³

Table 40: Grade 3-4 TEAEs in ≥5% of patients in the ripretinib group compared with BSC the group

TEAE	Ripretinib 150 mg QD any grade (n=85)	Ripretinib 150 mg QD grade 3/4 (n=85) [†]	BSC any grade (n=43)*	BSC grade 3/4 (n=43) [†]
Anaemia	16 (18.8%)	9 (10.6%)	8 (18.6%)	6 (14.0%)
Abdominal pain	34 (40.0%)	6 (7.1%)	13 (30.2%)	2 (4.7%)
Hypertension	13 (15.3%)	6 (7.1%)	2 (4.7%)	0

Abbreviations: BSC - Best supportive care; QD - Once a day; TEAE - Treatment-emergent adverse event.

* 44 patients were randomly assigned to BSC but 1 did not receive treatment

† Corresponding grade 3/4 TEAEs to TEAEs in ≥15% of patients receiving ripretinib

Source: von Mehren et al. 2021²³

Disutility values specific to patients with GIST associated with the AEs included in Table 41 could not be identified in literature searches. Disutility values were identified in previous NICE submissions for GIST (TA730) and colorectal cancer (TA439: review of TA176 and partial review of TA240).¹²⁸⁻¹³⁰ Disutility values for abdominal pain and hypertension were based on Doyle et al. (2008), in the context of advanced non-small cell lung cancer.¹³¹ The disutility for abdominal pain was assumed equal to that for chest pain. The disutility for anaemia originated from was based on Harrow et al.

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(2011), scaled to EQ-5D, as reported in Hoyle et al. (2013).^{132,133} The AE incidence for each treatment arm was multiplied by disutility values to obtain a total AE decrement for ripretinib and for BSC. Disutility associated with AEs is per event only and not related to the duration of the AE. All AEs were assumed to occur in the first cycle of the model and are summarised in Table 41 and Table 42.

Table 41: Ripretinib adverse event disutilities

Adverse event	Disutility	Probability	Total disutility
Anaemia	0.085	0.106	0.0080
Abdominal pain	0.069	0.071	0.0049
Hypertension	0.069	0.071	0.0049
Total			0.0188

Table 42: Best supportive care adverse event disutilities

Adverse event	Disutility	Probability	Total disutility
Anaemia	0.085	0.14	0.0119
Abdominal pain	0.069	0.047	0.0032
Hypertension	0.069	0	0
Total			0.0151

3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

Baseline health-related quality of life estimates from INVICTUS were not used directly in the model; rather, health status utility values were least square mean values from a mixed model of repeat measures (MMRM). After mapping EQ-5D-5L responses to EQ-5D-3L responses in line with Hernandez-Alava and Pudney (2022), the MMRM was applied, adjusting for treatment arm, treatment status, PF/PD health state and all two-way and three-way interactions as fixed effects, and with a compound symmetry within-subject correlation structure per treatment arm/ treatment status/health state combination.¹²⁰ As such, health state utility values reflected all EQ-5D measurements taken while patients were within each partition of the model. Beyond the MMRM approach, no further adjustments were made to values as they were input into the

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model. The model also incorporates an age adjustment for health state utility values, and utilities therefore vary over time based on a multiplier derived from general population EQ-5D estimates reported by Hernandez-Alava et al. (2022).¹³⁴

The cost-effectiveness analysis included four partitions: PF, PD on treatment, PD off treatment, and PD BSC. The PF partition represents patients at the start of the trial who have not experienced a progression event. This utility value was generated for both trial arms as a weighted average of patients randomised to ripretinib and those randomised to BSC. Clinicians at a UK advisory board agreed that it was reasonable to assume that patients start from the same baseline, irrespective of their randomisation.¹¹⁸ Clinicians also agreed that the assumed PF value for fourth-line ripretinib (0.722) should be slightly lower than that for 3L regorafenib (0.767 in TA488).^{38,101}

The PD partition is split into PD on and off treatment as justified in Section 3.2.2. Clinicians agreed that it was logical to calculate the PD on treatment value using observations from all patients receiving post progression ripretinib, including those originally randomised to the BSC arm but who crossed over upon progression, as both populations are receiving ripretinib and have experienced progression. Additionally, clinicians felt that patients with disease progression and receiving ripretinib (PD on-treatment) are clinically closer, in terms of HRQoL, to those in the progression-free state as compared with those who have progressed and are no longer on active treatment (PD off-treatment).^{38,118} In the base case analysis, a higher utility value is therefore allocated to PD on treatment vs PD off treatment.^{4,18,38} Patients no longer receiving active treatment after progression (PD off-treatment), irrespective of their randomised treatment arm and whether they received post-progression ripretinib, were deemed likely to have similar quality of life. Therefore, health state utility values for PD off treatment and PD BSC were assumed to be the same in the base case. A value of 0.624 was considered reasonable by clinicians, given that the observed difference between PF and PD off-treatment utility values for ripretinib (-0.098) is comparable to that used for regorafenib in TA488 (-0.120).

Table 43 summarises the final utility values used in the cost-effectiveness model in the base case.

Table 43: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% CI	Reference	Justification
PF	0.722 (0.2171)	0.684 – 0.759	Section 3.4.1 Health-related quality-of-life data from clinical trials (page 129)	Calculated from INVICTUS, in line with the NICE reference case and reflective of the patient population considered in this submission
PD (BSC)	0.624 (0.2838)	0.540 – 0.708		
PD on treatment	0.699 (0.2176)	0.656 – 0.741		
PD off treatment	0.624 (0.2838)	0.540 – 0.708		
Grade 3-4 AEs				
Anaemia	-0.085	NA	Section 3.4.4 Adverse reactions (page 133)	Identified through targeted published literature search or assumed equivalent to published estimate for a similar AE
Abdominal pain	-0.069	NA		
Hypertension	-0.069	NA		

Abbreviations: AE - Adverse event; BSC - Best supportive care; CI – Confidence intervals; NA - Not available; NICE - National Institute for Health and Care Excellence; PD - Progressed disease; PF - Progression-free; SD - Standard deviation.

In the previous ripretinib NICE appraisal (TA881), the ERG considered it appropriate to use the GRID trial PD utility (0.647). While the base case analysis was based exclusively on utility values derived from INVICTUS as a single, homogeneous data source, the GRID trial PD utility was explored in a scenario analysis as it was also likely to be representative of the average HRQoL level experienced by patients with advanced GIST who have progressed disease and are receiving BSC alone.^{18,38}

3.5 Cost and healthcare resource use identification, measurement and valuation

Appendix G describes how relevant cost and healthcare resource data were identified.

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3.5.1 Intervention and comparators' costs and resource use

Drug-related costs considered include the acquisition and administration costs for ripretinib + BSC, and BSC only.

Drug acquisition costs

Ripretinib

Ripretinib is available in 50 mg capsules and the list price per 30-day supply is £18,400. Ripretinib pricing has been included 'per pack' in line with NICE guidance.¹³⁵ The model supports the inclusion of a PAS in calculation of the drug costs for ripretinib. The licensed ripretinib dosing is 150 mg once daily. However, as patients in INVICTUS were permitted to escalate to BID ripretinib after disease progression, the model includes an input to capture the cost of BID ripretinib in a proportion of patients in the post progression- on-treatment partition. This BID costing is implemented using a pack-wastage-adjusted tablet price of ripretinib to avoid double counting of pack wastage at the time of progression. An assumption that 50% of patients with progressed disease received the BID dose was explored in a scenario analysis based on UK clinician opinion on the likely proportion of patients who would be expected to dose escalate to BID administration after progression (Section 2.6).

BSC

BSC costs were calculated from NICE TA488 (for regorafenib), the most recent recommended technology appraisal (TA) in GIST; TA488 used a clinician survey to estimate the proportion of patients treated with pain medication.¹⁰¹ These clinicians were based in the UK, and so BSC costs from TA488 are assumed to be more appropriate to the English setting than those approximated from concomitant medications taken in the BSC arm of INVICTUS. Pain management costs were applied across both arms (ripretinib and BSC). Dosing as per TA730/TA488 was combined with costs from the British National Formulary (BNF) from January 2025 as presented in Table 44.^{101,136} The assumed dose for each medication was based on the respective SmPC maintenance dose for the most common indication. In instances where the maintenance dose was a range, conservatively, the lowest dose was assumed. If the

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maintenance dose was not stated, half of the maximum dose was assumed. Prescription Cost Analysis data was used to identify the most commonly prescribed dosage form for each medication.¹³⁷

Calculated BSC costs per 28-day cycle are presented in Table 45. A scenario was explored whereby BSC costs were approximated from concomitant medications taken in the BSC arm of INVICTUS, with dosing and costs retrieved from the BNF in January 2025,^{19,136} as presented in Table 44.

Table 44: Pain Management costs as per TA730/TA488

Drug, dose	% patients (PF)	% patients (PD)	Unit	Units per pack (N)	Cost per pack	Units per cycle	Cost per 28-day cycle (PF)	Cost per 28-day cycle (PD)
Co-codamol, 2 (30/500 mg) QDS	18.0%	22.0%	30/500 mg tablet	100	£4.03	224	£1.62	£1.99
Tramadol, 100 mg QDS	12.0%	14.0%	50 mg capsule	100	£2.37	224	£0.64	£0.74
Paracetamol, 1g QDS	33.0%	38.0%	500 mg tablet	100	£2.16	224	£1.60	£1.84
Morphine sulfate immediate release, 30 mg every 4 hours	20.0%	29.0%	10 mg tablet	56	£5.31	168	£3.19	£4.62
			20 mg tablet	56	£10.61	168	£6.37	£9.23
Dexamethasone, 4 mg OD	11%	19%	4 mg tablet	50	£111.12	28	£6.84	£11.82
						Total	£20.26	£30.24

Abbreviations: OD - Once daily; PD - Progressed disease; PF - Progression-free; QDS - Four times a day; TA - Technology appraisal.

Table 45: Concomitant medications across ripretinib and BSC arms used in the base-case

Drug, dose	% patients (BSC)	% patients (ripretinib)	Unit	Units per pack (N)	Cost per pack	Units per cycle	Cost per 28-day cycle (BSC)	Cost per 28-day cycle (ripretinib)
Paracetamol, 500 mg QDS	60.5%	42.4%	500 mg tablet	100	£2.16	112	£1.46	£1.03
Oxycodone, 100 mg m/r BD	34.9%	31.8%	80 mg/mr tablet	56	£200.39	56	£69.94	£63.72
			20 mg m/r tablet	56	£50.08	56	£17.48	£15.93
Fentanyl, 50 µg patch every 72 hours	9.3%	12.9%	50 µg patch	5	£33.66	9	£5.84	£8.11
Morphine sulfate 10 mg every 4 hours	18.6%	11.8%	10 mg/5 ml oral solution, 1 ml	300	£7.22	840	£3.76	£2.38
Hydromorphone, 1.3 mg every 4 hours	14.0%	7.0%	1.3 mg tablet	56	£8.82	168	£3.70	£1.85
Amoxicillin, 500 mg TDS	11.6%	3.5%	500 mg capsule	21	£1.51	21	£0.18	£0.05
Ciprofloxacin, 500 mg BD	11.6%	3.5%	500 mg tablet	10	£0.97	14	£0.16	£0.05
Loperamide hydrochloride, 6 mg daily	16.3%	8.2%	2 mg capsule	30	£0.77	15	£0.06	£0.03

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Drug, dose	% patients (BSC)	% patients (ripretinib)	Unit	Units per pack (N)	Cost per pack	Units per cycle	Cost per 28-day cycle (BSC)	Cost per 28-day cycle (ripretinib)
Ondansetron, 8 mg every 12 hours	23.3%	34.1%	8 mg tablet	10	£1.58	10	£0.37	£0.54
Ibuprofen, 200 mg TDS	14.0%	20.0%	Ibuprofen tablet	84	£2.63	84	£0.37	£0.53
Sodium chloride 0.9% IV solution, 1500 ml/24 hours once a month	11.6%	16.5%	0.9% IV infusion solution, 9 mg/1 ml, 500 ml	1	£3.57	3	£1.24	£1.77
Ranitidine, 300 mg daily	25.6%	31.8%	75 mg tablet	12	£0.30	112	£0.72	£0.89
Macrogol, 2 sachets daily	34.9%	32.9%	sachet	30	£8.59	28	£2.80	£2.64
Docusate sodium, 100 mg BD	11.6%	12.9%	100 mg capsule	30	£2.14	14	£0.12	£0.13
Sennoside A+b, 7.5 mg OD	14.0%	12.9%	7.5 mg daily	60	£1.70	7	£0.03	£0.03
Metoclopramide, 10 mg TDS	18.6%	22.4%	10 mg tablet	28	£0.83	21	£0.12	£0.14
Potassium chloride tabs, 600 mg BD	16.3%	12.9%	600 mg tablet	100	£67.28	56	£6.14	£4.86
Diazepam, 2 mg OD	30.2%	11.8%	2 mg tablet	28	£0.67	28	£0.20	£0.08

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Drug, dose	% patients (BSC)	% patients (ripretinib)	Unit	Units per pack (N)	Cost per pack	Units per cycle	Cost per 28-day cycle (BSC)	Cost per 28-day cycle (ripretinib)
Levothyroxine, 50 µg OD	34.9%	29.4%	50 µg tablet	28	£0.64	28	£0.22	£0.19
Vitamin D, 800 IU OD	16.3%	12.9%	800 IU capsule	30	£3.60	28	£0.55	£0.43
						Total	£115.45	£105.36

Abbreviations: BD - Twice a day; BSC - Best supportive care; IU - International units; IV - Intravenous; m/r - Modified release; OD - Once a day; QDS - Four times a day; TDS – Three times a day.

Source: NICE, BNF, Deciphera DOF, INVICTUS Clinical Study Report.^{19,136}

3.5.2 Health-state unit costs and resource use

The approach to health state costs is based on TA730 and TA488.^{101,128} Resource use frequencies were originally based on a survey conducted in 2013 involving 15 clinicians from the UK. These frequencies were re-evaluated in 2016 by two consultant oncologists based in UK clinical practice.¹⁷

The ripretinib marketing authorisation is independent of mutational status, therefore no additional diagnostic testing is required. According to UK clinical practice guidelines, all patients with GIST are routinely tested for mutations on diagnosis.⁴ Therefore, costs associated with diagnostic testing have not been included in the model.

Table 46 presents the one-off costs of tests taken by a proportion of patients before treatment in addition to palliative surgical resection and palliative radiotherapy given to relieve or prevent symptoms. It was assumed that all patients require regular resource use, monitoring and tests as reported in Table 47.

Table 46: One-off health state resource use

Resource	Unit cost	Mean proportion of patients		Source
		PF	PD (on treatment)	
CT scan	£123.25	Ripretinib: 85% BSC: 24%	-	NICE TA488; NHS reference costs 2023/24 (weighted average of CT scan of three areas, with contrast, RD26Z)
MRI scan	£171.05	Ripretinib: 12% BSC: 1%	-	NICE TA488; NHS reference costs 2023/24 (weighted average of MRI codes RD01A to RD07Z)
Full blood count	£3.09	Ripretinib: 92% BSC: 56%	-	NICE TA488; NHS reference costs 2023/24 (haematology DAPS05)
Liver function test	£1.95	Ripretinib: 92% BSC: 49%	-	NICE TA488; NHS reference costs 2023/24 (clinical biochemistry DAPS04)
Palliative resection	£6,090.28	10%	10%	NICE TA488; (PD assumed to be same as PF); NHS reference costs 2023/24 (weighted average of costs for malignant GI tract disorders with a single intervention: FD11D, FD11E, FD11F)
Palliative radiotherapy	£366.00	20%	20%	NICE TA488; (progressed assumed to be same as PFS); NHS reference costs 2023/24 (weighted average of adult medical specialist palliative care attendance costs: SD01A, SD02A, SD03A, SD04A)

Abbreviations: BSC - Best supportive care; CT - Computed tomography; GI - Gastrointestinal tract; MRI – Magnetic resonance imaging; NICE - National Institute for Health and Care Excellence; PD - Progressed disease; PF - Progression-free; TA - technology appraisal.

Table 47: Regular resource use per patient: monitoring and tests

Resource	Unit cost	PF		PD*		Source
		Mean number of weeks between tests	Frequency per 28-day cycle	Mean number of weeks between tests	Frequency per 28-day cycle	
CT scan	£123.25	Ripretinib: 12.1 BSC: 18.9	Ripretinib: 0.33 BSC: 0.21	14.5	0.28	NICE TA488; NHS reference costs 2023/24 (weighted average of CT scan of three areas, with contrast, RD26Z)
MRI scan	£171.05	Ripretinib: 19.9 BSC: 18.0	Ripretinib: 0.20 BSC: 0.22	8.0	0.50	NICE TA488; NHS reference costs 2023/24 (weighted average of MRI codes RD01A to RD07Z)
Full blood count	£3.09	Ripretinib: 6.4 BSC: 10.9	Ripretinib: 0.63 BSC: 0.37	8.8	0.45	NICE TA488; NHS reference costs 2023/24 (haematology DAPS05)
Liver function test	£1.95	Ripretinib: 6.4 BSC: 11.2	Ripretinib: 0.63 BSC: 0.36	9.4	0.43	NICE TA488; NHS reference costs 2023/24 (clinical biochemistry DAPS04)
Outpatient care visit	£193.00	Ripretinib: 6.2 BSC: 7.9	Ripretinib: 0.65 BSC: 0.51	6.9	0.58	NICE TA488 (frequency for patients on BSC); NHS reference costs 2023/24 (WF01A code 370 WF01A consultant led non-admitted face-to-face attendance, follow-up)

*BSC; ripretinib on treatment and ripretinib off treatment. Abbreviations: BSC - Best supportive care; CT - Computed tomography; MRI – Magnetic resonance imaging; NICE - National Institute for Health and Care Excellence; PD - Progressed disease; PF - Progression-free; TA - Technology appraisal.

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3.5.3 Adverse reaction unit costs and resource use

The health effects of TEAEs were modelled via the incidence of grade 3-4 AEs; those occurring at a frequency of $\geq 5\%$ in either treatment arm were included in the evaluation as they are likely to be associated with costs that affect decision making. Costs were sourced from the 2023/24 NHS National Cost Collection.¹³⁸ Grade 3-4 TEAE rates were obtained from INVICTUS.

Table 40 presents the TEAE rates applied in the model. The base case costs associated with treating and managing TEAEs used in the model are presented in Table 48.

Table 48: Cost of resolving TEAEs in the economic model

Grade 3-4 TEAE	2023/24 NHS National Cost Collection	NHS currency code description
Anaemia	£989.48	Weighted average of SA01G:SA01K, SA03G:SA03H, SA04H:SA04L and SA05G:SA05J – total HRGs
Abdominal pain	£679.32	Weighted average of FD05A and FD05B – total HRGs
Hypertension	£760.02	EB04Z – total HRGs

Abbreviations: HRG - Healthcare resource group; NHS – National Health Service; TEAE - Treatment-emergent adverse event.

3.5.4 Miscellaneous unit costs and resource use

The approach to end-of-life costs was aligned with TA730 and TA488.^{7,128} The introduction of end-of-life costs does not affect undiscounted model outcomes as the model effectively has a lifetime time horizon. All patients have died in both arms by the time horizon, so the total undiscounted cost associated with end-of-life care is identical for each arm. The costs associated with end-of-life care are relevant to discounted model outcomes when mortality differs between arms, since a larger proportion of end-of-life costs are incurred later in the arm with lower mortality. To capture this, end-of-life costs were incorporated into the cost-effectiveness model.¹³⁹

End-of-life costs were taken from NICE TA488 and inflated to 2024 prices using HCHS/NHSCII indices.¹⁴⁰ The original cost was taken from the study of Abel et al. Company evidence submission template for ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments (review of TA881) [ID6496]

(2013) that presents data for a cohort of hospice patients in South West England.¹⁴¹ All patients had life-limiting disease and were referred to the hospice for specialist palliative care. The resulting weighted cost for end-of-life care of £10,926.76 presented in Table 49 was incurred by each patient on death.

Table 49: Base-case end-of-life cost

Detail on end-of-life	Proportion of patients	Cost, inflated to 2024 values
Death in hospital	16%	£14,856.09
Death outside of hospital	84%	£10,163.52
Weighted total		£10,926.76

In line with advice from NICE, a scenario is included using estimates for end-of-life costs from Round et al. (2015).¹⁴² The terminal care costing study incorporated Bayesian modelling using data from the literature and publicly available datasets. Breast, colorectal, lung and prostate cancer were considered. The costs used in the cost-effectiveness model scenario analysis relate to direct costs borne by the health and social care sectors, in line with the perspective recommended in the NICE reference case. The resulting cost for end-of-life care of £7,777.76 in Table 50 was allocated to each patient upon death.

Table 50: Scenario analysis end-of-life cost

Detail on end-of-life	Mean cost, inflated to 2024 values
End-of-life cost healthcare	£5,439.19
End-of-life cost social care	£2,338.57
Total	£7,777.76

3.6 Severity

Patients with advanced GIST previously treated with three or more TKIs (Section 3.3) are anticipated to experience an additional 0.247 QALYs on BSC (over a period of 0.375 life years and based on a log-logistic model of OS in INVICTUS). This would correspond to a 98.0% proportional shortfall vs an age- and sex-matched UK population, who would be anticipated to experience an average of 12.68 QALYs based Company evidence submission template for ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments (review of TA881) [ID6496]

on an adjusted, limited-dependent, variable mixture model (ALDVMM) of 2014 HSE data (Hernandez-Alava et al.; the York QALY Shortfall Calculator reference case). Table 51 and 52 present key features and inputs of the QALY shortfall analysis.

Sensitivity analyses around general population estimates (using: EQ-5D-5L to EQ-5D-3L mapping from Hernandez-Alava et al. with HSE 2017-18 data; EQ-5D-5L to EQ-5D-3L mapping from van Hout et al. with HSE 2017-18 data; and a health state profile-based model using the 1995 Measurement and Valuation of Health [MVH] Report) showed that no general population estimates would yield less than a 98.0% proportional shortfall in patients with advanced GIST receiving BSC after three or more TKIs (Table 53).^{119,143}

Sensitivity analyses around alternative survival distributions (exponential, Weibull, Gompertz, log logistic, and generalised gamma) to model INVICTUS BSC data showed only small differences in estimated QALY gain (0.18-0.24 QALYs; Table 53). Sensitivity analyses incorporating different patient characteristics were conducted in two alternative populations of patients with advanced GIST from the GRID trial and Bulusu et al.^{41,91}

Ripretinib would therefore be eligible for a 1.7x QALY weight based on the proportional shortfall rule, and analyses of this appear robust to changes in both the general population, BSC QALY estimates, and GIST population characteristics.

Table 51: Summary features of the QALY shortfall analysis

Factor	Value (table reference)	Section reference
OS model	Log-logistic; two-stage-adjusted simple model with recensoring	Section 3.3
Sex distribution	56.6% male (Table 8)	Section 3.2 and 3.9
Starting age (years)	60.1 (Table 8)	Section 3.2 and 3.9

Abbreviations: QALY- Quality-adjusted life years.

Table 52: Summary of health state benefits and utility values for QALY shortfall analysis

State	Utility value: mean (SD)	Undiscounted life years
Progression-free	0.722 (0.2171)	0.1425
Progressed disease	0.624 (0.2838)	0.2424

Abbreviations: QALY- Quality-adjusted life years.

Table 53: Summary of the QALY shortfall analysis

Analysis	Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall
Base case	12.68	0.25	12.43 QALYs or 98.0%
Hernandez-Alava et al. mapping with HSE 2017-18 data	12.34	0.25	12.09 QALYs or 98.0%
van Hout et al. mapping with HSE 2017-18 data	12.42	0.25	12.17 QALYs or 98.0%
MVH value set with health state profiles	12.26	0.25	12.01 QALYs or 98.0%
MVH value set with HSE 2012 and 2014 data	12.67	0.25	12.42 QALYs or 98.0%
Exponential OS model for BSC	12.68	0.23	12.45 QALYs or 98.2%
Weibull OS model for BSC	12.68	0.19	12.49 QALYs or 98.5%
Gompertz OS model for BSC	12.68	0.18	12.50 QALYs or 98.6%
Lognormal OS model for BSC	12.68	0.24	12.44 QALYs or 98.1%
Generalised gamma OS model for BSC	12.68	0.21	12.47 QALYs or 98.3%

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Analysis	Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall
GRID trial patient characteristics (median 60 years old, 64% male)	12.66	0.25	12.42 QALYs or 98.1%
Bulusu et al. patient characteristics (median 64 years; 52% male)	11.32	0.25	11.08 QALYs or 97.8%

Abbreviations: BSC - Best supportive care; HSE - Health Survey for England; MVH - Measurement and Valuation of Health; OS - Overall survival; QALY - Quality-adjusted life year.

3.7 Uncertainty

Ripretinib was granted orphan marketing authorisation by the MHRA, with advanced GIST being rare with a prevalence of less than 3 in 10,000 people.²² In the UK, the eligible population for ripretinib will be approximately 173 patients. The sample size of INVICTUS (n=129) may be considered small relative to other indications and this may be the cause of uncertainties in the data. However, relative to other pivotal RCTs in this patient population (regorafenib GRID trial, n=199) and given the prevalence of the disease, the sample size of INVICTUS is considered appropriate for decision-making.⁸

There is considerable uncertainty around the clinical effects of ripretinib BID dosing and likely utilisation in UK clinical practice. As ripretinib is the last-line treatment for this patient population, dose escalation was offered at disease progression to enable patients to have a treatment option beyond ripretinib QD. IPDE was seen in 44 of the 85 patients randomly assigned to ripretinib (15 January 2021 data cut).⁷⁴ The base case analysis assumes that ripretinib will only be used within the licensed indication and in line with the licensed dose of 150 mg QD. However, the extent of usage outside of the licensed dose that may occur in routine clinical practice, and what the clinical outcomes with such use would be, is a source of uncertainty. Clinicians stated that in a scenario where BID dosing was routinely commissioned, IPDE would occur in

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approximately 40% of all patients starting ripretinib which is lower than the 52% in INVICTUS.³⁸ This would be expected as the tolerability for BID dosing would probably be lower in routine clinical practice, given the strict inclusion criteria for INVICTUS resulting in a population that is often fitter than that in routine clinical practice.

3.8 Managed access proposal

Not applicable.

3.9 Summary of base-case analysis inputs and assumptions

3.9.1 Summary of base-case analysis inputs

A summary of variables applied in the economic analysis is presented in Table 54.

Table 54: Summary of variables applied in the economic model

Parameter	Value	Measurement of uncertainty and distributions			Reference to location in submission
		Lower bound	Upper bound	Within PSA varied by	
Model setup					
Time horizon, years	40	Varied in scenario analyses		N/A	Section 3.2
Age, years	60.1	N/A	N/A	N/A	
Percentage male	56.6%	34.0%	77.8%	Beta	
Discount rate costs	3.5%	Varied in scenario analyses		N/A	
Discount rate outcomes	3.5%	Varied in scenario analyses		N/A	
Clinical inputs					
Ripretinib - PFS	Log-normal	Varied in scenario analyses		Log-normal	Section 3.3
Ripretinib - OS	Log-logistic	Varied in scenario analyses		Log-normal	
Ripretinib – TTD after progression	Exponential	Varied in scenario analyses		Log-normal	
BSC - PFS	Log-normal	Varied in scenario analyses		Log-normal	
BSC - OS	Log-logistic	Varied in scenario analyses		Log-normal	
Cost inputs					
Ripretinib pre-treatment cost (£)	129.93	84.08	185.59	Gamma	Section 3.5
BSC pre-treatment cost (£)	33.98	21.99	48.53	Gamma	
Ripretinib cost per cycle (£)	17,173.33	N/A	N/A	N/A	Section 3.5

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Parameter	Value	Measurement of uncertainty and distributions			Reference to location in submission
		Lower bound	Upper bound	Within PSA varied by	
Ripretinib compliance	100%	N/A	N/A	Beta	
Ripretinib relative dose intensity	96.50%	94.71%	97.93%	Beta	
BSC cost per cycle (ripretinib arm) PFO n (£)	20.26	13.11	28.93	Gamma	Section 3.5
BSC cost per cycle (ripretinib arm) PD (£)	30.24	19.57	43.20	Gamma	
BSC cost per cycle PF (£)	20.26	13.11	28.93	Gamma	
BSC cost per cycle PD (£)	30.24	19.57	43.20	Gamma	
BSC compliance	100%	N/A	N/A	N/A	
BSC relative dose intensity	100%	N/A	N/A	N/A	
Ripretinib PF health state total cost (£)	202.79	131.24	289.67	Gamma	Section 3.5
Ripretinib PDOff health state total cost (£)	233.64	151.20	333.74	Gamma	
Ripretinib PDOn health state total cost (£)	233.64	151.20	333.74	Gamma	
BSC PF health state total cost (£)	163.65	105.90	233.75	Gamma	
BSC PD health state total cost (£)	233.64	151.20	333.74	Gamma	
Ripretinib palliative care cost PF (£)	682.23	441.50	974.50	Gamma	

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Parameter	Value	Measurement of uncertainty and distributions			Reference to location in submission
		Lower bound	Upper bound	Within PSA varied by	
Ripretinib palliative care cost PD (£)	682.23	441.50	974.50	Gamma	
BSC palliative care cost PF (£)	682.23	441.50	974.50	Gamma	
BSC palliative care cost PD (£)	682.23	441.50	974.50	Gamma	
End of life cost (£)	10926.76	7071.23	15607.83	Gamma	
Ripretinib AE total cost (£)	207.08	134.01	295.79	Gamma	
BSC AE total cost (£)	170.46	110.31	243.48	Gamma	
Utility values					
Utility: PF	0.722	0.684	0.760	Beta	Section 3.5
Utility: PD (BSC)	0.624	0.539	0.709	Beta	Section 3.5
Utility: PDO _n	0.699	0.651	0.747	Beta	Section 3.5
Utility: PDO _{ff}	0.624	0.539	0.709	Beta	Section 3.5
Ripretinib AE total disutility	0.019	0.012	0.027	Beta	Section 3.5
BSC AE total disutility	0.015	0.010	0.022	Beta	

Abbreviations: AE - Adverse event; BSC - Best supportive care; N/A - Not applicable; OWSA - One-way sensitivity analysis; PD - Progressed disease; PF - Progression-free survival; PSA - Probabilistic sensitivity analysis.

3.9.2 Assumptions

A summary of modelling assumptions is provided in Table 55, divided by the aspect of the cost-effectiveness model.

Table 55: Model assumptions

Category	Assumption	Justification
Population and comparators	BSC is the most appropriate comparator for ripretinib	BSC was the comparator in INVICTUS, in line with the NICE scope, as clinicians agreed it is established clinical management and the most appropriate comparator.
	INVICTUS reflects the patient population receiving ripretinib and BSC in the UK who have received prior treatment with three or more kinase inhibitor inhibitors, including imatinib	Inclusion criteria in INVICTUS were aligned with the UK marketing authorisation. Ten UK patients were enrolled in INVICTUS (7.75%). Clinicians agreed that the INVICTUS population is generalisable to the UK.
Model structure and settings	Partitioned survival model	Reflective of the pivotal events that occur in well-accepted model structure in oncology.
	OS, PFS and post-progression treatment discontinuation are modelled independently	Structural independence of the OS, PFS, and post-progression treatment discontinuation models is inherent to the partitioned survival model approach; however, all models were derived from the same data with access to mortality, progression, and treatment discontinuation data.
	UK NHS and PSS perspective	In line with the NICE reference case.
	Lifetime horizon	In line with the NICE reference case and previous NICE appraisals in GIST.
	3.5% <i>per annum</i> discount rate for costs and outcomes	In line with the NICE reference case.
Clinical effectiveness	The two-stage approach provides an appropriate method to account for crossover in INVICTUS	Patients are only able to crossover following disease progression; confounders measured at or close to the time of progression; trial randomised until progression.

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Category	Assumption	Justification
	Log-normal distribution provides an appropriate PFS extrapolation for ripretinib and BSC	Of the distributions tested, log-normal distribution had the lowest (i.e. most favourable) AIC and BIC in the ripretinib arm. Plausibility of 10-year extrapolation was confirmed in a UK clinician advisory board.
	Log-logistic distribution provides an appropriate OS extrapolation for ripretinib and BSC	Of the distributions tested, log-logistic distribution had the lowest (i.e. most favourable) combined AIC and BIC. Clinicians agreed that the shape of the log-logistic empirical hazard function was likely to be most reflective of clinical reality.
	Exponential distribution provides an appropriate extrapolation of treatment discontinuation after progression	Of the distributions tested, exponential showed the best fit to the post-progression treatment discontinuation composite endpoint by both AIC and BIC. Clinicians agreed that the shape of the exponential empirical hazard function was likely to be most reflective of clinical reality.
	Grade 3-4 TEAEs are included and assumed to occur in the first cycle of the model	TEAEs are likely to occur very soon after treatment and require acute care. This is consistent to the modelling approaches adopted in several oncology TAs (e.g., TA429 and TA561).
	No administration costs for ripretinib	Ripretinib is an oral treatment and would not be anticipated to incur administration costs from the NHS or PSS perspective.
	No subsequent lines of therapy are captured, with only BSC costs applied following progression	Ripretinib is expected to be the last line of therapy in UK clinical practice, as confirmed by clinicians.
Cost and resource use inputs	No indirect costs are applied	In line with the NICE reference case.
	Ripretinib costs captured after progression based on treatment discontinuation in INVICTUS	Post-progression use of ripretinib is likely to reflect clinical practice as the last line of treatment for advanced GIST.

Abbreviations: AIC - Akaike information criterion; BIC - Bayesian information criterion; BSC - Best supportive care; GIST - Gastrointestinal stromal tumour; NHS - National Health Service; NICE - National Institute for Health

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and Care Excellence; OS - Overall survival; PFS - Progression-free survival; PSS - Personal social services; TEAE - Treatment emergent adverse event.
Source: Clinical advisory boards held in 2022, 2024 and 2025^{38,70,118}

3.10 Base-case results

Total costs, LYs, QALYs, and incremental cost per QALY gained for ripretinib versus BSC are presented in Table 56. In the base-case analysis, ripretinib generates [REDACTED] incremental QALYs and [REDACTED] incremental costs over a 40-year time horizon compared with BSC, resulting in an ICER (incremental cost-effectiveness ratio) of £28,836 per QALY gained including the PAS discount and using a 1.7 severity weighting for QALY calculations. Disaggregated base-case results are presented in Appendix H. These results are driven by the clinically meaningful benefits of ripretinib vs BSC seen in INVICTUS, specifically a 5.3-month improvement in median PFS, an 11.9-month improvement in median OS and an 8-month improvement in the maintenance of HRQoL.^{16,23}

Table 56: Base-case deterministic incremental cost-effectiveness analysis results with the PAS applied

Technologies	Costs (£)	LYG	QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
BSC	[REDACTED]	0.375	[REDACTED]	-	-
Ripretinib	[REDACTED]	3.104	[REDACTED]	-	-
Incremental	[REDACTED]	+2.729	[REDACTED]	28,836	28,836

Abbreviations: BSC - Best supportive care; ICER - Incremental cost-effectiveness ratio; LYG - Life years gained; PAS – Patient access scheme; QALYs - Quality-adjusted life years

The expected net health benefits of ripretinib versus BSC using willingness-to-pay thresholds of £20,000 and £30,000 per QALY are presented in Table 57.

Table 57: Net health benefit of ripretinib versus BSC

Technology	Total cost (£)	Total QALYs	Incremental cost (£)	Incremental QALYs	NHB at £20,000 (QALYs)	NHB at £30,000 (QALYs)
BSC	■	■	-	-	-	-
Ripretinib	■	■	■	■	■	■

Abbreviations: BSC - Best supportive care; NHB - Net health benefit; QALYs - Quality-adjusted life years.

3.11 Exploring uncertainty

3.11.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analyses (PSAs) were conducted to explore the impact of model parameter uncertainty on the results. Ten thousand simulations were performed, which combined give a distribution of incremental results and consequently an assessment of the robustness of the cost-effectiveness results. PFS and OS remain independent within the PSA as per a standard PSM. For gender proportions, event rates, compliance, relative dose intensity and utilities, a beta distribution was used to restrict draws to between 0 and 1. For costs, a gamma distribution was fitted to prevent values less than zero. Treatment costs remained fixed.

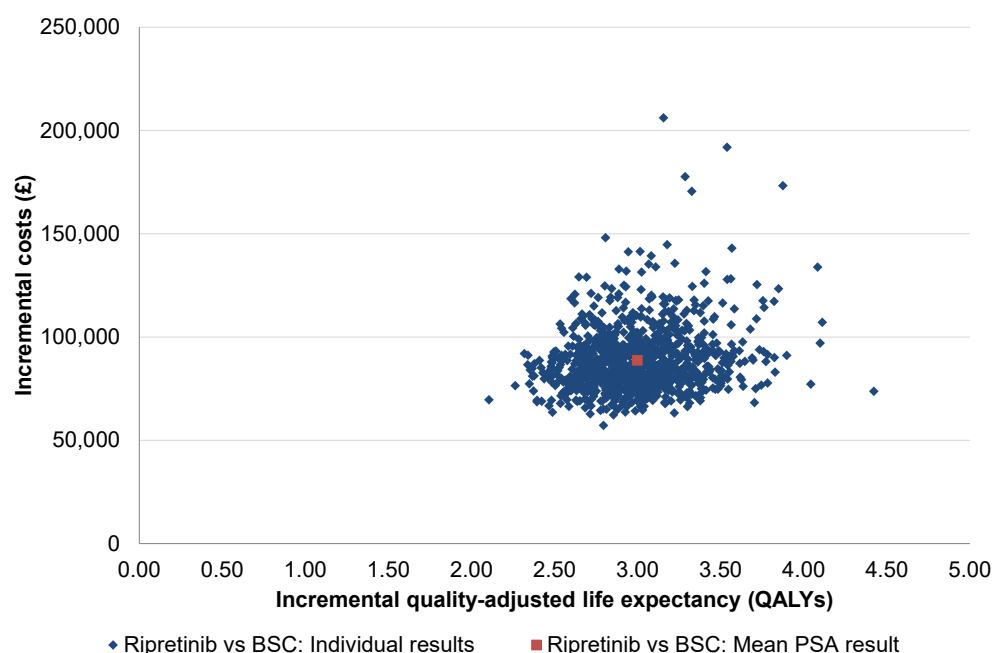
Total costs, QALYs and the incremental cost per QALY gained with ripretinib versus BSC are presented in Table 58. An incremental cost-effectiveness plane scatter plot, cost-effectiveness acceptability curve, and cost-effectiveness acceptability frontier were produced to graphically illustrate the level of variability and uncertainty in the results, as shown in Figure 33, Figure 34, and Figure 35 respectively. In the PSA, all results fell in the northeast quadrant of the cost-effectiveness plane, representing increased costs and quality-adjusted life expectancy with ripretinib versus BSC. At a willingness-to-pay threshold of £30,000 per QALY, there was a 57.2% likelihood of ripretinib being cost-effective versus BSC. Variation between deterministic and probabilistic analyses was minimal, with the ICER only differing by £757 per QALY (£29,593 per QALY in the probabilistic sensitivity analysis versus £28,836 per QALY in the deterministic base case).

Table 58: Probabilistic sensitivity analysis results for ripretinib versus BSC

Technologies	Mean cost (95% CrI), £	Mean QALYs (95% CrI)	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
BSC	████	████	-	-
Ripretinib	████	████	-	-
Incremental	████	████	29,593	29,593

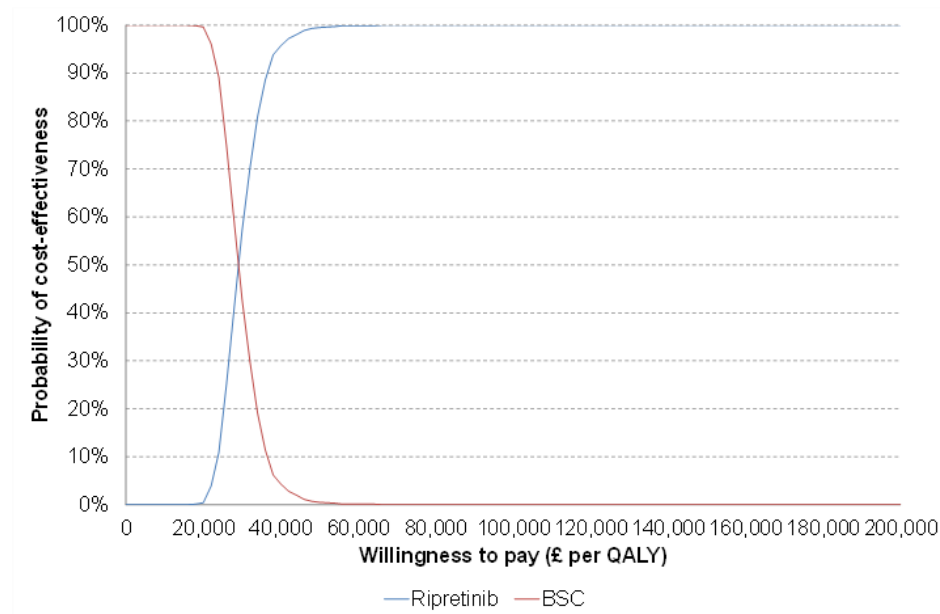
Abbreviations: BSC - Best supportive care; CrI - Credible interval; ICER - Incremental cost-effectiveness ratio; QALYs - Quality-adjusted life years.

Figure 33: Incremental cost-effectiveness scatterplot showing incremental costs and QALYs with ripretinib versus BSC from 1,000 probabilistic sensitivity analysis iterations



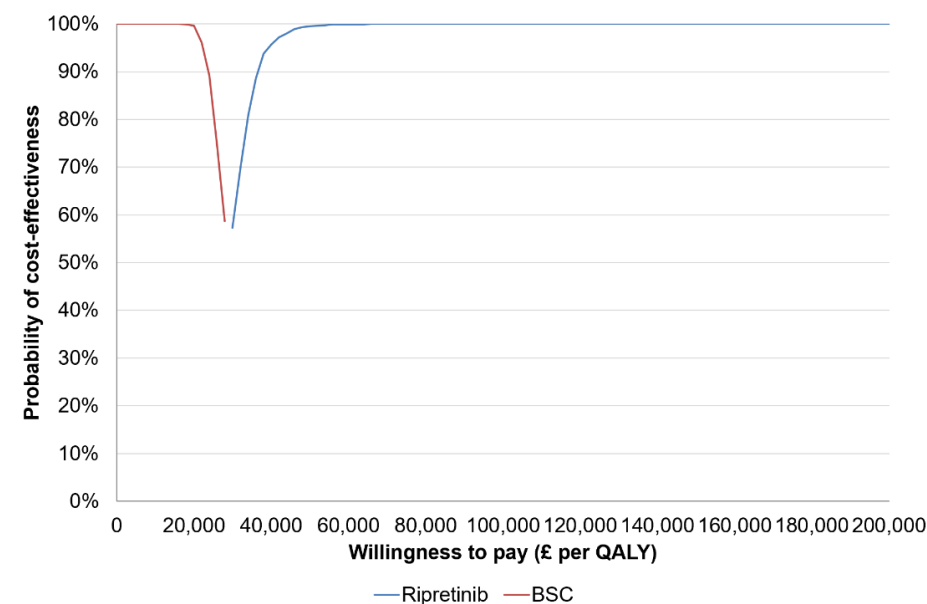
Abbreviations: BSC - Best supportive care; PSA - Probabilistic sensitivity analysis; QALYs - Quality-adjusted life years.

Figure 34: Cost effectiveness acceptability curve for ripretinib versus BSC showing the likelihood of cost effectiveness over a range of willingness to pay thresholds spanning £0 per QALY gained to £200,000 per QALY gained



Abbreviations: BSC - Best supportive care; QALY - Quality-adjusted life year.

Figure 35: Cost-effectiveness frontier for ripretinib versus BSC showing the likelihood of cost-effectiveness over a range of willingness-to-pay thresholds spanning £0 per QALY gained to £200,000 per QALY gained



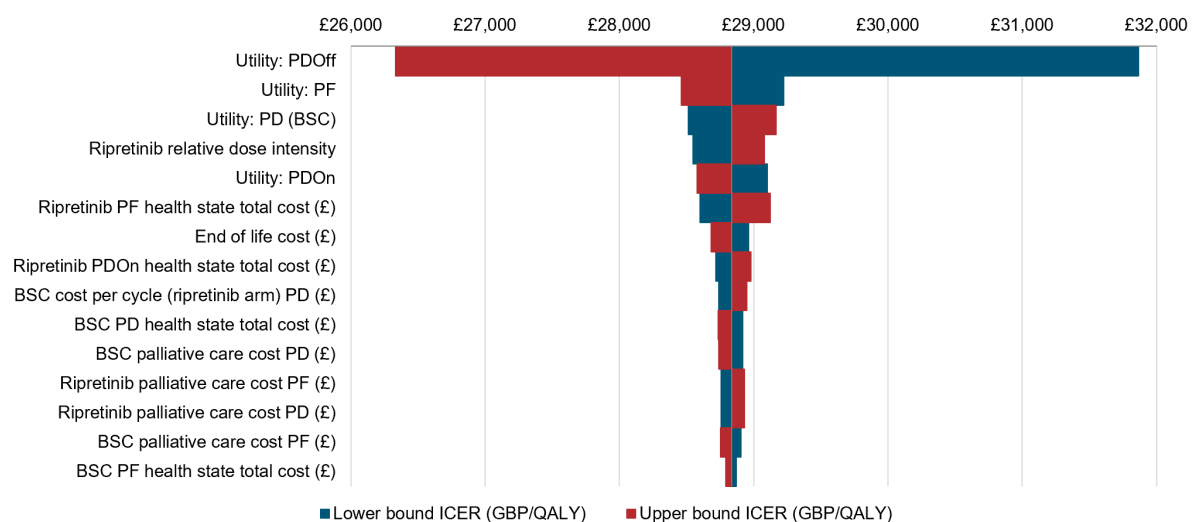
Abbreviations: BSC - Best supportive care; QALY - Quality-adjusted life year.

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3.11.2 Deterministic sensitivity analysis

Deterministic one-way sensitivity analysis (OWSA) was conducted to explore the degree of uncertainty in the model results arising from variation in individual model parameters. The OWSA was conducted by allocating a 'low' and a 'high' value to each parameter; where confidence intervals were available, the low value was the lower bound and the high value was the upper bound of the 95% CI; in the absence of CI data, variable was altered by +/- 20%. A tornado diagram presenting the 15 most sensitive parameters is presented in Figure 36, with tabulated results in Table 59. The model was most sensitive to the PDOff health state utility value, which resulted in an increase in ICER to £31,865 per QALY at the lower bound, and a reduction in ICER to £26,333 per QALY at the upper bound. This is because patients remain in the off-treatment PD partition for considerably longer (■■■■ years vs ■■■■ years in the on-treatment partition in the base case analysis). PDOff therefore has a substantial effect on QALY estimates in the ripretinib arm, particularly as the PDOff utility has no influence on the BSC arm.

Figure 36: Tornado diagram showing one-way sensitivity analysis results



Abbreviations: BSC - Best supportive care; ICER - Incremental cost-effectiveness ratio; PD - Progressed disease; PDOOn - Progressed disease on treatment; PDOff - Progressed disease off treatment; PF, Progression-free; QALY - Quality-adjusted life year.

Table 59: Tabulated one-way sensitivity analysis results

Parameter	Lower bound ICER (£/QALY)	Upper bound ICER (£/QALY)	Difference (£/QALY)
Utility: PDOff	31,865	26,333	5,533
Utility: PF	29,222	28,460	762
Utility: PD (BSC)	28,514	29,165	652
Ripretinib relative dose intensity	28,548	29,081	534
Utility: PDOOn	29,100	28,577	523
Ripretinib PF health state total cost (£)	28,600	29,122	523
End of life cost (£)	28,963	28,682	281
Ripretinib PDOOn health state total cost (£)	28,716	28,981	265
BSC cost per cycle (ripretinib arm) PD (£)	28,741	28,951	210
BSC PD health state total cost (£)	28,920	28,734	187
BSC palliative care cost PD (£)	28,917	28,738	179
Ripretinib palliative care cost PF (£)	28,756	28,932	176
Ripretinib palliative care cost PD (£)	28,757	28,932	175
Utility: PDOff	31,865	26,333	5,533
Utility: PF	29,222	28,460	762

Abbreviations: BSC - Best supportive care; ICER - Incremental cost-effectiveness ratio; PD - Progressed disease; PDOOn - Progressed disease on treatment; PDOff - Progressed disease off treatment; PF, Progression-free; QALY - Quality-adjusted life year.

3.11.3 Scenario analysis

Table 60 details scenario analyses results for ripretinib versus BSC.

Table 60: Scenario analysis results

Analysis	BSC QALYs	Ripretinib QALYs	Incremental QALYs	BSC costs (GBP)	Ripretinib costs (GBP)	Incremental costs (GBP)	ICER (GBP/QALY)
Base case	████	████	████	████	████	████	£28,836
0% discounting	████	████	████	████	████	████	£24,851
6% discounting	████	████	████	████	████	████	£31,149
End-of-life costs	████	████	████	████	████	████	£28,939
OS model							
OS: exponential	████	████	████	████	████	████	£37,434
OS: Weibull	████	████	████	████	████	████	£37,602
OS: Gompertz	████	████	████	████	████	████	£26,247
OS: Log-normal	████	████	████	████	████	████	£29,538
OS: Generalised gamma	████	████	████	████	████	████	£28,974
PFS model							
PFS: exponential	████	████	████	████	████	████	£28,611
PFS: Weibull	████	████	████	████	████	████	£28,604
PFS: Gompertz	████	████	████	████	████	████	£28,640
PFS: Log-logistic	████	████	████	████	████	████	£30,079
PFS: Generalised gamma	████	████	████	████	████	████	£28,648
PFS+TTD model							
PFS+TTD: Weibull	████	████	████	████	████	████	£28,674
PFS+TTD: Gompertz	████	████	████	████	████	████	£28,939

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Analysis	BSC QALYs	Ripretinib QALYs	Incremental QALYs	BSC costs (GBP)	Ripretinib costs (GBP)	Incremental costs (GBP)	ICER (GBP/QALY)
PFS+TTD: Log-logistic	████	████	████	████	████	████	£33,487
PFS+TTD: Log-normal	████	████	████	████	████	████	£32,092
PFS+TTD: Generalised gamma	████	████	████	████	████	████	£29,301
Crossover approach (OS log-logistic models unless otherwise noted)							
OS: Unadjusted	████	████	████	████	████	████	£43,575
OS: two-stage adjusted simple without recensoring	████	████	████	████	████	████	£28,876
OS: two-stage adjusted complex without recensoring	████	████	████	████	████	████	£29,993
OS: two-stage adjusted complex with recensoring	████	████	████	████	████	████	£29,775
OS: RPSFTM-adjusted without recensoring	████	████	████	████	████	████	£29,727
OS: RPSFTM-adjusted with recensoring	████	████	████	████	████	████	£28,237
OS: RPSFTM-adjusted with common treatment effect relaxed ($k_i=0.5$; Weibull)	████	████	████	████	████	████	£27,470
OS: RPSFTM-adjusted with common treatment effect relaxed ($k_i=0.5$)	████	████	████	████	████	████	£31,104

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Analysis	BSC QALYs	Ripretinib QALYs	Incremental QALYs	BSC costs (GBP)	Ripretinib costs (GBP)	Incremental costs (GBP)	ICER (GBP/QALY)
Utilities							
GRID utility (0.647) for progressed disease (BSC) and progressed disease on-treatment	████	████	████	████	████	████	£28,195
GRID utility (0.647) for all progressed disease partitions	████	████	████	████	████	████	£28,469
Same utility in progressed on- and off-treatment partitions (0.624 from INVICTUS)	████	████	████	████	████	████	£29,251
IPDE OS adjustments							
Two-stage adjustment (simple covariate adjustment; log-normal distribution; STR=3.45)	████	████	████	████	████	████	£28,209
Two-stage adjustment (complex covariate adjustment; generalised gamma distribution; STR=2.72)	████	████	████	████	████	████	£28,278
Time-varying Cox proportional hazards model (treatment covariate only; HR=1.58)	████	████	████	████	████	████	£29,347

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Analysis	BSC QALYs	Ripretinib QALYs	Incremental QALYs	BSC costs (GBP)	Ripretinib costs (GBP)	Incremental costs (GBP)	ICER (GBP/QALY)
Time-varying Cox proportional hazards model (all covariates; HR=1.37)	████	████	████	████	████	████	£29,162
Open-label BID vs QD OS analysis (non-progressors + IPDE progressors; log-logistic)	████	████	████	████	████	████	£31,371
Open-label BID vs QD OS analysis (non-progressors + QD progressors; log-logistic)	████	████	████	████	████	████	£30,142
IPDE cost adjustments (as requested by NHS during a commercial surgery)							
Cost of ripretinib BID captured in 50% of patients remaining on treatment after progression	████	████	████	████	████	████	£32,671

Abbreviations: BID - Twice a day; BSC - best supportive care; HR - hazard ratio; IPDE - inpatient dose escalation; OS - overall survival; PFS - progression-free survival; QALY - quality-adjusted life year; QD - quaque die (every day/once daily); RPSFTM - rank-preserving structural failure time model; STR - survival time ratio; TTD - time to discontinuation.

Of the scenario analyses in Table 60, the approaches to modelling OS have the largest influence on ICER. Removing any adjustment to OS for crossover from BSC to ripretinib has the largest effect on the ICER, increasing it to £43,575 per QALY. Switching the OS model in both arms to use Weibull or exponential distributions (and retaining the base case crossover adjustment) increases the ICER to £37,602 per QALY and £37,434 per QALY, respectively; neither distribution was adopted in the base case analysis owing to poorer goodness-of-fit to the data than the log-logistic distribution in both treatment arms and by both measures (AIC and BIC). Furthermore, the predicted 10-year survival with these curves was deemed too low given the 10-year survival data for other TKIs in advanced GIST. Conversely, switching the OS model to use the Gompertz distribution reduces the ICER by £2,589 per QALY from the base case to £26,247 per QALY. Across all scenarios, 21 yielded ICERs that fell below a WTP threshold of £30,000 per QALY, while 9 yielded ICERs above a £30,000 per QALY threshold.

Scenarios in which alternative utility values were employed all yielded ICERs below a £30,000 per QALY threshold, including an analysis that assumed no utility benefit of staying on treatment after progression. This latter scenario was not adopted in the base case as it is contrary to the utility values observed in INVICTUS in patients with progressed disease receiving treatment versus those not receiving treatment (0.699 versus 0.624, respectively). Correspondingly, maintenance of HRQoL (median TUDD) was longer than median PFS in INVICTUS. Clinicians validated this assumption, noting that patients with disease progression receiving ripretinib would be closer in terms of HRQoL to those in the progression-free state than those who have progressed and are no longer on active treatment.

All approaches to adjusting for IPDE had a relatively modest effect on the ICER. In the case of the two-stage adjustment and time-varying Cox proportional hazards model, this was likely driven by a relatively limited exposure to the elevated mortality hazard (i.e. in the on-treatment PD state only). The effect in the two open-label BID vs QD analyses was driven by different mortality hazard trajectories over time; patients in the 'non-progressors + IPDE progressors' analysis had a lower mortality risk than 'non-progressors + QD progressors' early in the analysis; this increased to higher than Company evidence submission template for ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments (review of TA881) [ID6496]

the QD progressors group later in the analysis, ultimately yielding very similar ICERs (£31,371 per QALY in 'non-progressors + IPDE progressors' vs £30,142 per QALY in 'non-progressors + QD progressors'). An analysis was requested during a NHS Commercial Surgery in which 50% of patients in the on-treatment progressed disease partition incurred the cost of BID ripretinib yields an ICER of £32,671 per QALY gained; however, this approach deviates from the licensed ripretinib dose of 150 mg QD and was therefore not adopted in the base case. Clinicians agreed this approach reflects a scenario where BID is routinely commissioned and, if so, they expected 50% of patients who progressed on ripretinib (40% of the total population to initiate ripretinib) to dose escalate.

3.12 Subgroup analysis

Patients with advanced GIST who have had at least 3 prior therapies, including imatinib, or have documented intolerance to these treatments comprise a small population with high unmet need. As such, further subgroup analyses have not been performed.

3.13 Benefits not captured in the QALY calculation

The health economic analysis did not capture potential effects of the burden of advanced GIST on caregivers or of death of the patient and bereavement on caregiver and family quality of life. Data to inform on such analyses are not available but such effects are likely to exist though are not currently quantifiable. The maintenance of patients' HRQoL, including physical and role function, while receiving ripretinib suggests a potential reduction in dependence on carers, thereby also improving carer QoL.

The effect of having an additional line of therapy available after regorafenib on patient QoL was also not captured due to a lack of suitable data. Having an additional therapy line would give patients hope that they can live a somewhat normal life for longer than currently possible. Hope is a factor that does not come into consideration in traditional health technology assessments (HTA); however, an ISPOR taskforce found that it has

positive value, and although difficult to quantify should be considered by HTA authorities.¹⁴⁴

3.14 Validation

Validation of cost-effectiveness analysis

A two-stage quality control (QC) process was used during development of the cost-effectiveness model. The first QC occurred after an empty model was constructed with dummy placeholder data and was intended to: test the structure of the model; ensure that core calculations such as background mortality were correct; and confirm that no naming errors or common Excel formula errors were present. The second QC process occurred on model completion when it was put through a number of 'binary tests', whereby key variables are set to zero and results checked for face validity. The model also underwent a second structural test to ensure that calculations and formulae were correct. A final face validity check ensured that the context in which the variables were used was clinically and theoretically sound. The process of QC was conducted by an experienced modeller who was not the original model builder, with findings recorded against a QC checklist. The document was passed to the modelling team who implemented the QC recommendations, recording their agreement/disagreement. Where disagreement existed, the project director ensured third-party consensus resolution.

INVICTUS is the largest mature dataset currently available informing on patients treated with ripretinib. At the 15 January 2021 data cut utilised in the model, 54% (n=46/85) of patients in the ripretinib group and 82% (n=36/44) of patients in the placebo group had died.²³ External validation of the intervention in a comparable patient population is challenging given the rarity of the disease and lack of active comparators; however, the Royal Marsden Expanded Access Program (Section 2.6) reported a median OS of 14.0 months (95% CI 9.9 to NA months) compared with the 18.2 months (95% CI 13.1 to 30.7 months) in INVICTUS.⁶⁹ Data from other studies in the advanced GIST setting are available (A618-1004 [sunitinib] and GRID [regorafenib]), these studies were conducted in earlier lines of therapy and do not include ripretinib treatment arms to validate the extrapolation.^{8,145}

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To validate the analysis, median PFS (ripretinib and BSC) and OS (ripretinib) predicted by the model were compared with data from INVICTUS (15 January 2021 data cut-off), as shown in Table 61. Predicted landmark survival rates compared with the INVICTUS Kaplan-Meier curve are presented in Table 62. Comparison demonstrates that the model closely predicts the clinical data for ripretinib and BSC.

Table 61: Summary of model predicted outcomes compared with INVICTUS data, ITT population

Outcome	Clinical trial result, median weeks	Model result, median weeks (based on linear interpolation within cycles)
Ripretinib		
PFS	27.57	████
OS	79.14	████
BSC		
PFS	4.14	████

Abbreviations: BSC – Best supportive care; OS – Overall survival; PFS – Progression-free survival.

Table 62: Summary of model predicted landmark rates compared with clinical data, ITT population

Distribution	Weeks				
	26	52	78	104	130
Ripretinib					
PFS KM data	51%	22%	12%	5%	2%
PFS extrapolated data	████	████	████	████	████
OS KM data	84%	65%	52%	43%	41%
OS extrapolated data	████	████	████	████	████
	13	26	39	52	65
BSC					
PFS KM data	13%	3%	3%	N/A	N/A
PFS extrapolated data	████	████	████	████	████

Abbreviations: BSC - Best supportive care; KM - Kaplan-Meier; N/A - Not applicable; OS - Overall survival; PFS – Progression-free survival.

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Opinion from an expert in crossover adjustment was sought to identify the most appropriate method to adjust for patients crossing over following disease progression, from BSC to the ripretinib. It was deemed that the two-stage approach using the time of progression as the secondary baseline was most appropriate to adjust for crossover. In TA488, the ERG deemed the switching analyses results to be generally robust to the choice of method and were satisfied with the approach taken.¹⁰¹

UK clinician advisory boards including specialists in the treatment of GIST were conducted to validate specific modelling inputs and assumptions including: OS crossover adjustment and extrapolation (including the effect of dose escalation); composite PFS and TTD extrapolation; appropriate comparator therapy; treatment beyond progression; utility values; and subsequent treatment.

3.15 Interpretation and conclusions of economic evidence

In the base-case analysis, ripretinib generates 2.962 incremental QALYs and incremental costs over a 40-year time horizon compared with BSC, resulting in an ICER of £28,836 per QALY gained including the PAS discount and using a 1.7 severity weighting for QALY calculations. At a willingness-to-pay threshold of £30,000 per QALY, there was a 57.2% likelihood of ripretinib being cost-effective vs BSC. Variation between deterministic and probabilistic analyses was minimal, with the ICER only differing by £757 per QALY. The model was most sensitive to the PDOff health state utility value, which resulted in an increase in ICER to £31,865 per QALY at the lower bound, and a reduction in ICER to £26,333 per QALY at the upper bound. However, scenario analyses varying utility values indicated minimal impact on the ICER. Key areas of uncertainty identified by the scenario analyses are the approaches to modelling OS and the impact of BID on clinical outcomes and cost. This is not unexpected given the limitations in data in these areas and highlight the main limitations in the model analysis. In particular, several statistical methods were explored to quantify the uncertainty around the effect of IPDE on OS, but gave contradictory results. However, incorporation of outcomes from the various approaches into the model yielded ICERs that were relatively consistent. Finally, the base case assumptions were validated externally through clinician advisory boards to

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ensure they were clinically plausible and would represent UK clinical practice as closely as possible.

This economic analysis is highly relevant to clinical practice in England: all unit costs were identified from UK-specific sources; INVICTUS included ten patients from the UK; and clinicians were supportive of the applicability of INVICTUS data to a UK population with advanced GIST. The main strength of the analysis was the use of a single, homogeneous data source as the basis of modelling the three main clinical endpoints in the model: progression, treatment discontinuation after progression, and death.

In conclusion, based on this analysis (incorporating a 1.7x severity multiplier based on the proportional QALY shortfall in the BSC population versus the general population), ripretinib represents a cost-effective option relative to BSC for the treatment of patients in England with advanced GIST who have received prior treatment with three or more kinase inhibitors, including imatinib.

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INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal Ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments (review of TA881)

[ID6496]

Summary of Information for Patients (SIP)

May 2025

File name	Version	Contains confidential information	Date
ID6496 Ripretinib Summary of Information for Patients_noCON	1.0	No	28 May 2025

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the [Health Technology Assessment International – Patient & Citizens Involvement Group](#) (HTAi PCIG). Information about the development is available in an open-access [IJTAHC journal article](#)

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Ripretinib (Qinlock®)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

QINLOCK is used to treat adults with gastrointestinal stromal tumour (GIST), a rare type of cancer of the digestive system including the stomach and bowel, that has:

- spread to other parts of the body or cannot be removed by surgery
- been treated with at least 3 previous cancer medicines, including imatinib.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The MHRA granted marketing authorisation on the 20th of December 2021.

Link: [Ripretinib Public Assessment Report](#)

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Nothing to disclose

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Gastrointestinal stromal tumours (GISTs) are rare cancers that develop in the digestive system. Most GISTs start in the stomach or small bowel, but they can develop anywhere along the length of the digestive system (gastrointestinal tract). For example, they may also start in the gullet (oesophagus) or the back passage (rectum).^{1,2} Most GISTs are usually caused by alterations in the proto-oncogene c-KIT (KIT) or the platelet-derived growth factor receptor alpha (PDGFRA) gene. These alterations allow the tumour cells to grow.³

There are around 900 new cases of GIST each year in the UK.⁴ GISTs are most common in people aged 60 to 65. As GIST progresses, it can cause serious symptoms. The symptoms depend on the size of the tumour and where it is in the digestive system and so vary from person to person. Symptoms may include: discomfort or pain in the tummy (abdomen), blood in your poo (stools) or vomit, weight loss for no obvious reason, feeling tired and weak².

One of the key factors in determining the outlook for GIST cancer is the stage at which it is diagnosed. For patients with advanced GIST, the chance of being alive at 5 years after diagnosis is 53%.⁵

People living with advanced GIST often experience a considerable impact on their daily lives, affecting their work, relationships, and ability to carry out everyday activities.⁸ As the disease worsens, people may experience a sharp decline in their quality of life, including mental and social difficulties.⁹ Additionally, the side effects of current treatment can make day-to-day activities challenging.¹⁰

GIST can have an impact on family members, friends, and caregivers, too. Caregivers often handle many tasks: giving emotional support, cooking, cleaning, driving to appointments, helping with medicines, and sorting out bills. They may also help you dress, bathe, and stay connected with friends and family. Caregiving can be a difficult and consuming job.¹¹

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

If your GP suspects you have GIST, they will refer to a specialist doctor for further testing. The primary tests to confirm a diagnosis of GIST include imaging scans, such as a computed tomography (CT) scan, and through a tissue sample (biopsy). A firm diagnosis of GIST can only be made by a pathologist looking at the tumour tissue with a microscope. Hence, there needs to be a tissue sample. A biopsy may be done endoscopically using an instrument passed into the stomach or intestines through the mouth, or anus.

The diagnosis of GIST is confirmed if:

- A tumour is identified in the gastrointestinal tract
 - Imaging tests reveal the presence of a tumour in the stomach, small intestine, or other parts of the gastrointestinal tract
- The cells of tumour carry specific markers

- A biopsy is performed to confirm the tumour type. The tumour cells are analysed for markers, such as CD117 and DOG1, which are commonly present in GISTs
- Genetic changes indicate GIST
 - The laboratory will also test cells from the biopsy or surgery to look for genetic changes in the tumour cells. These changes are called mutations. Finding a positive c-KIT (CD117) or PDGFRA enzyme receptor abnormality can confirm a diagnosis of GIST^{4,12}

No additional diagnostic tests will be required to identify patients for treatment with ripretinib.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
 - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
 - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Advanced GIST is considered a chronic cancer, meaning the tumours may never fully disappear. Patients often require ongoing treatment to control the disease over time. Most GISTs (around 85%) have a mutation in a protein called KIT, which causes the cancer cells to grow and divide continuously. Targeted therapy drugs, known as tyrosine kinase inhibitors (TKIs), are used to block these signals.²

The standard first-line treatment for GIST is imatinib. If this becomes ineffective or causes significant side effects, patients may receive second-line therapy with sunitinib, followed by third-line therapy with regorafenib.¹³

Current treatment pathway for advanced GIST (first-line to fourth-line):



Source: Judson I et al. 2017.¹²

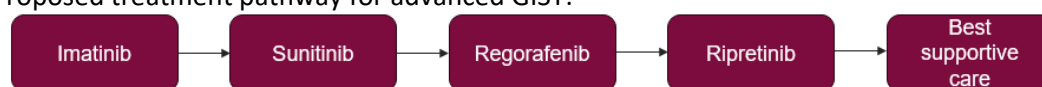
Some types of GIST do not respond well to imatinib, and over time, the cancer cells can change (mutate) in ways that help them avoid the effects of treatment. This is known as becoming resistant, meaning the treatment no longer works as well. As a result, the tumour may start to grow again.

Beyond third-line treatment: Best supportive care (BSC)

There are no recommended drugs available after regorafenib. For patients who are no longer receiving benefit from regorafenib, they are offered BSC. This care focuses on easing symptoms, managing side effects, and preserving the best possible quality of life. This may include the use of pain relievers, anti-nausea medications, and other supportive therapies.¹⁴⁻¹⁷ Patients are

recommended to try and enrol in clinical trials if possible.⁶ Ripretinib would be positioned as a fourth-line treatment option, offering a further targeted drug option before BSC.

Proposed treatment pathway for advanced GIST:



2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Sarcoma UK insights

Sarcoma UK reports that once patients with GIST have exhausted current treatment options, they may have "on average just weeks to live" if no further therapy is available, highlighting a critical unmet need.¹⁸

The 2020 National Sarcoma Patient Survey had 1,117 responses including patient, family and carers. Of these, 14% of the responses concerned GIST. The aim of the survey was to understand the patient, family and carer experience of living with sarcoma. The survey found that 95% of patients with GIST reported negative mental health effects related to their diagnosis and treatment, with many also experiencing isolation, anxiety, and sadness. Furthermore, patients with GIST were reported to be the least likely amongst sarcoma patients to receive the emotional support they needed, possibly due to the rarity of the disease.¹⁹

The survey also reported, more than half of carers of patients with GIST had to stop working or studying, either temporarily or permanently. Every carer also reported feeling frequently or constantly anxious or depressed since the patient's GIST diagnosis highlighting the immense impact advanced GIST has on caregivers and family.¹⁹

Life Raft Group Canada (LRGC) insights

The LRGc conducted 11 interviews with patients with metastatic GIST to capture the real-world experiences of those undergoing treatment. These interviews revealed that patients experience a wide range of severe side effects from imatinib, sunitinib, and regorafenib, with 39 distinct side effects identified across these treatments. Patients described "horrible" effects from imatinib such as uncontrollable diarrhoea, swelling, cramps, and chronic pain that significantly compromised their quality of life. Similarly, sunitinib was described as "extremely toxic... I had really bad diarrhoea constantly... wicked foot blisters that made it hard to walk. I couldn't walk. It was so bad." These firsthand accounts emphasise the challenge of daily life on GIST treatments, despite their role in extending survival.²⁰

Patient input from first NICE technology appraisal

Patients highlighted the improved side effect profile of ripretinib in comparison to previous therapies. One patient shared: "Ripretinib is better than regorafenib because the side effects are

more manageable. I had to take regorafenib for three weeks then have a week off, and by week three the PPE [palmar-plantar erythrodysesthesia] and diarrhoea side effects were so severe I was able to do very little other than rest with my feet raised.”

Patients have also reported that whilst using ripretinib they are able to maintain a normal life, continuing to work, travel, and exercise. They emphasise the importance of these activities, as it allows them to lead their lives, rather than feeling defined solely by their cancer.⁹

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Current therapies (imatinib, sunitinib, regorafenib) are all tyrosine-kinase inhibitors (TKIs) and they work by blocking the KIT and PDGFRA receptor proteins on the surface of GIST cancer cells. These receptors normally control cell growth, but when they become altered (mutated) they drive uncontrolled cell multiplication leading to the development of tumours. TKIs help to keep these mutated proteins turned off by blocking them. Unfortunately, we now know that GIST cells quite often mutate again and find a way round the block meaning the tumour can start to grow again.^{3,13}

Ripretinib works differently compared with previous TKIs and binds to a different place on the protein than other TKIs. This means that for patients where imatinib, sunitinib and regorafenib have become ineffective, ripretinib may still work and can improve survival. Ripretinib offers patients with GIST an effective fourth-line treatment that can work even for tumours that have many mutations that make them resistant to the other TKIs.²¹⁻²³

Links: [Summary of Product Characteristics](#) and [Patient Information Leaflet](#)

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

No

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Ripretinib will be prescribed for you by a doctor experienced in using anticancer therapies.

The recommended daily dose is **three 50 mg tablets** (150 mg) once daily.

Take the tablets at the **same time each day** with or without food. Swallow the tablets whole with a glass of water and do not chew, split, or crush the tablets. Do not take any tablets that are broken, cracked, or otherwise damaged due to unknown effects of taking tablet that are not whole.

If you have to take certain other medicines at the same time as ripretinib, your doctor may change your dose to three 50 mg tablets (150 mg) twice daily.

You will usually take ripretinib as long as you are benefitting from it and not suffering unacceptable side effects; however, your doctor may reduce your dose or may decide to interrupt or stop the treatment temporarily or permanently if necessary.

If you have liver or kidney problems

- While you are being treated with ripretinib, your doctor will monitor your liver or kidney function more closely.

If you take more ripretinib than you should

- If you have accidentally taken too many tablets, **seek urgent medical attention.**

If you forget to take ripretinib

- What to do if you forget to take this medicine, depends on when you remember the dose that has been forgotten. If it is:
 - 8 hours or less (4 hours or less for 150 mg twice per day doses) after the time it should have been taken, take the missed dose as soon as you remember. Then take the next dose as usual.
 - more than 8 hours after (more than 4 hours for 150 mg twice per day doses) the time it should have been taken, skip the missed dose. Then take the next dose at the usual time.
 - Do not take a double dose to make up a forgotten dose.

If you are sick when taking ripretinib

- If you are sick (vomiting) after taking this medicine, do not take an additional dose, but carry on as normal. Take your next dose of tablets the next day at the usual time and tell your doctor you have been sick.

If you have any further questions on the use of this medicine, ask your doctor.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

INVICTUS

The INVICTUS study investigated ripretinib as a treatment for patients with advanced GIST who needed a fourth (or greater) line of therapy.

The main aim of the study was to see if treatment with ripretinib could affect tumour growth and extend survival time compared with placebo treatment (a pill with no active ingredient).^{13,17}

Study characteristics:

Location	The INVICTUS study took place in 29 hospitals in 12 countries, including two in the UK	
Population	Adult patients with advanced GIST who had progressed on or were intolerant to imatinib, sunitinib, and regorafenib	
Patient group size	129 participants 85 patients in the ripretinib arm 44 patients in the placebo arm	
Intervention	Ripretinib + best supportive care	
Comparators	Placebo + best supportive care	
Key inclusion criteria	- Males or females ≥ 18 years - Confirmed diagnosis of GIST - Patients must have progressed on imatinib, sunitinib, and regorafenib or have documented intolerance to any of these TKIs - At least 1 measurable tumour - Adequate organ function and bone marrow reserve - An Eastern Cooperative Oncology Group (ECOG) score of 0–2: this measures how the disease impacts daily living; scores range from 0 (fully active with no restrictions) to 5 (dead)	
Key exclusion criteria	Patients who received anticancer therapy within 14 days prior to the study	
Start date	22 August 2016	
Completion date	18 August 2022	

Abbreviations: GIST; Gastrointestinal Stromal Tumour

Source: Blay J et al. 2020.¹⁷

Key efficacy outcomes (to determine how ripretinib effects tumour growth)

- Progression-free survival (PFS): How long people were able to live their daily lives before a scan showed the tumour had started growing/worsening again or before they died
- Overall survival (OS): How long people stayed alive after joining the study
- Objective response rate (ORR): How many patients responded to the treatment, this includes:¹⁷
 - Complete response - all signs of cancer have disappeared
 - Partial response - a reduction in the size of the tumour
- Rate of stable disease (SD): How many patients experienced no change in the size of tumour

Quality of life assessments (to determine how well patients feel when they take ripretinib)

The study also measured health-related quality of life (HRQoL) using the following questionnaires

which patients answered throughout the study:

- EORTC QLQ-C30 - assesses physical and role functioning in patients with cancer specifically
- EQ-5D-5L – measures general health status
- EQ-VAS - measures general health status.²⁴

Safety assessment (to determine how safe ripretinib is for patients): included the number of side effects (adverse events [AEs]) and any side effects that led to dose reduction, treatment interruption, or discontinuation.^{17,22}

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Key findings from INVICTUS

Progression-Free Survival (PFS)

The main goal of the INVICTUS study was to measure how long patients lived without their disease getting worse, or before dying.

- Half of the participants receiving ripretinib survived for 6.3 months or longer before their cancer got worse, compared with 1.0 month or longer for participants receiving placebo^{13,17}

Objective Response Rate (ORR)

This measures how many patients responded to the treatment. This endpoint shows how effective the treatment is in reducing or eliminating tumours.

- Of the 85 participants receiving ripretinib, 8 had partial responses – meaning that the size of their tumor was reduced by 30% or more (as defined in a set of rules called modified Response Evaluation Criteria in Solid Tumors [mRECIST]). No participants in the placebo arm had partial response.
- After the responses were analysed, they were not considered statistically conclusive.
- More importantly for patients and clinicians is the stable disease (SD) rate, as SD is known to predict survival. At 6 weeks, 66% of ripretinib-treated patients experienced SD, which remained at 47% at 12 weeks, in contrast to 20% and 5% in the placebo group, respectively.
- This shows that ripretinib is more effective at controlling the disease.^{13,17}

Overall Survival (OS)

This measures how long patients lived after starting treatment.

- Half of the participants receiving ripretinib survived overall for 18.2 months or longer from the start of therapy, compared with 6.3 months or longer for participants receiving placebo; this included participants on placebo who were permitted to take ripretinib when their disease worsened.²²

Limitations

- Some patients who initially started on placebo, started to take ripretinib after their disease had worsened. This means that the survival in the placebo arm may be overestimated given the benefit some of these patients likely received from ripretinib.

- When disease worsened, some patients started to take ripretinib at a double dose. This dose is not included in the marketing authorisation and may have impacted the survival demonstrated in the ripretinib arm. However, clinicians agree that the extent of the effect of the double dose on how long patients live is uncertain.¹⁵

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQoL-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs)**.

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Quality of life in the INVICTUS trial

On questionnaires that investigated quality of life, participants receiving ripretinib had stable scores up to treatment cycle 10 of treatment, while participants receiving placebo reported a decline in quality of life.

- These questionnaires included evaluations of physical function, everyday capabilities, and patient perceptions of their overall health and quality of life.

Across individual questionnaires, as measured from the start of treatment to the start of Cycle 2, ripretinib resulted in improved scores (a higher score means patients perceived their overall health and quality of life to be better) whereas scores in participants receiving placebo declined:²⁴

- Overall health (EQ-5D-5L VAS): Ripretinib improved scores by an average **+3.7 points**, whereas placebo fell **-8.9 points**
- Physical abilities (QLQ-C30 physical function): Ripretinib improved scores by an average **+1.6 points**, whereas placebo fell **-8.9 points**
- Everyday roles at work, home and socially (QLQ-C30 role function): Ripretinib improved scores by an average **+3.5 points**, whereas placebo fell **-17.1 points**.²⁴

Importantly, participants receiving ripretinib had a stable quality of life for about 8 months, whereas it began to drop after only 1 month on placebo.²⁴ Moreover, participants maintained HRQoL even when their disease worsened when receiving ripretinib. This underscores ripretinib's ability to preserve everyday functioning.^{25,26}

Participant who experienced hair loss (a common side effect of ripretinib) reported HRQoL scores that were comparable or slightly better to those of participants who did not, indicating that patients receiving ripretinib were not negatively impacted by this side effect.^{22,27}

Conclusion

Collectively, these findings show that ripretinib can not only prolong survival but also enable patients with advanced GIST to preserve their HRQoL for longer.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had

treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Ripretinib therapy is associated with some treatment-emergent side effects that are generally well controlled. Of patients receiving ripretinib in the INVICTUS trial, 5% discontinued ripretinib treatment due to side effects (vs. 2% in the placebo group).¹⁷

Clinicians have noted that ripretinib's side effects are generally mild to moderate and can be largely managed within specialist GIST/sarcoma clinics.⁹

Common side effects

The most common side effects of ripretinib, based on the INVICTUS trial:

	Ripretinib arm	Placebo arm
Hair loss (alopecia)	49%	2%
Muscle aches/pain (myalgia)	27%	9%
Nausea (feeling sick)	25%	2%
Tiredness (fatigue)	24%	14%
Palmar-plantar erythrodysesthesia (rash on the palms of the hands and soles of the feet)	21%	0%
Diarrhoea	20%	5%

Source: Blay J et al. 2020.¹⁷

Managing side effects

Interrupting treatment or reducing the dose may be necessary for some patients who experience side effects. If required, the recommended dose reduction is to 100 mg of ripretinib taken orally, once a day. If a patient cannot tolerate 100 mg per day, treatment should be permanently discontinued.

Serious side effects

Seek urgent medical attention if you experience any of the following serious side effects:

1. Skin problems (called PPES)
 - PPES is a very common side effect when taking this medicine. If you develop: redness, pain, swelling, or blisters on the palms of your hands or soles of your feet, your doctor may continue your treatment, change your dose or stop your treatment until your condition improves.
2. High blood pressure
 - High blood pressure is a very common side effect when taking this medicine. If you develop: headache, feeling of light-headedness, or dizziness, these may be symptoms of high blood pressure, your doctor may change your dose or stop your treatment until your condition improves.
3. Heart problems (heart failure)
 - Heart failure is a common side effect when taking this medicine. If you feel: very tired, are short of breath, have swollen feet and/or ankles, these may be symptoms of heart problems.

Talk to your doctor or pharmacist if you experience:

4. Skin cancer

- Treatment with ripretinib may result in certain types of skin cancer such as ‘cutaneous squamous cell carcinoma’ and ‘melanoma’. Tell your doctor if you notice any skin changes during treatment including a new wart, open sore or reddish bump that bleeds or does not heal, or a change in size or colour of a mole. Your doctor will check your skin when starting treatment with ripretinib and routinely during treatment.

Conclusion

Overall, ripretinib offers a manageable safety profile, with side effects that can typically be addressed through dose adjustments. Monitoring and managing these side effects effectively means most patients can continue benefiting from treatment whilst minimising discomfort.

Further information can be found in the ripretinib [Summary of Product Characteristics](#) and the [Patient Information Leaflet](#).

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Key benefits for patients

The results of INVICTUS showed that ripretinib provides a viable treatment option for patients with GIST who have already tried 3 or more different therapies. Ripretinib can potentially extend the time before a patient's cancer gets worse and can improve survival compared to placebo.^{13,22}

Despite advanced disease, ripretinib may allow patients to maintain their quality of life and functional status over a period of approximately 8 months, compared to the rapid decline seen in patients on placebo after just 1 month.²⁴

Ripretinib has a manageable safety profile for patients. Common adverse effects include alopecia, muscle aches/pains, nausea, and tiredness.¹⁷

Administered as once-daily oral tablets, ripretinib is easy for patients to incorporate into their daily routines.

Key benefits for caregivers and the community

Ripretinib has the potential to alleviate the emotional, financial and social burden on caregivers and their communities. Ripretinib's ability to extend survival without compromising the patient's well-being can reduce caregivers' fear and worry related to disease progression. Moreover, as ripretinib preserves functional status and maintains quality of life, it may reduce the need for intensive support, such as assistance with daily activities, and help patients regain some independence and as well as relieving caregivers of some of that responsibility.^{9,24}

Conclusion

Overall, ripretinib provides a much-needed further option for patients who have progressed on three previous lines of therapy. The introduction of ripretinib would offer hope to patients, carers and their communities.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Key considerations for patients

Like most cancer treatments, ripretinib can cause side effects. Whilst these are generally mild to moderate, they can still impact patients' day-to-day lives. Common side effects include alopecia, myalgia, nausea, fatigue and diarrhoea.¹⁷

In some cases, patients may need to adjust their dosage due to side effects, which may require regular monitoring and consultation with their healthcare team. This can add complexity to the treatment and may cause some uncertainty for patients.

Key considerations for caregivers and the community

Although ripretinib has a manageable safety profile, caregivers may still need to assist with managing any side effects. The emotional and physical burden of caring for a patient experiencing these side effects may still be significant.

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

How the model reflects the condition

This model calculates the additional cost of one healthcare intervention (ripretinib) compared to another (BSC), for a corresponding increase in health benefit. The model development was guided by clinical and health economic experts, ensuring its relevance and alignment with UK clinical practice for patients with advanced GIST after progression on three or more TKIs.⁶ The clinical benefits reflect those demonstrated in INVICTUS while the costs represent the average costs incurred to NHS England (NHSE) during the care of this patients with GIST.

Model structure

The model reflects how a patient disease progresses through different disease-related health

states. Health states represent the level of health and well-being of the patient at that point in time, informed by INVICTUS HRQoL data. Each health state is also associated with a different level of costs, informed by NHSE service costs. The amount of time a patient spends in each state is driven by data from INVICTUS.

The three key disease-related health states are:

1. Progression-Free (PF) – patients are alive without experiencing disease worsening on the current line of treatment
2. Progressed Disease (PD) – patients are alive but have experienced disease worsening on the current line of treatment
3. Death.

Modelling the impact of ripretinib on survival

Ripretinib is expected to extend survival by delaying disease worsening. The model estimates that ripretinib increases a patient's life expectancy by approximately 2.7 years compared to BSC alone. This reflects the significant survival benefits of ripretinib vs placebo observed in INVICTUS.^{17,22}

Modelling quality of life improvements

The HRQoL improvements with ripretinib were measured using EQ-5D-5L data from the INVICTUS trial. HRQoL was incorporated into the model through quality-adjusted life years (QALYs).

** A QALY, or quality-adjusted life year, is a way of measuring both how long someone lives and how good their health is during that time—one QALY means one year of life in perfect health.*

The model estimates that 3 QALYs per patient are gained with ripretinib compared to BSC alone. This reflects the ability of ripretinib to maintain patient HRQoL for an extended period compared to BSC, even after disease worsening, as demonstrated in INVICTUS.^{22,24}

Modelling treatment costs

The model includes all relevant costs associated with ripretinib treatment, including the drug cost, disease management costs, and costs associated with side effects. Ripretinib is estimated to cost an additional £85,414 per patient compared to BSC alone.

Exploring uncertainty in the model

To understand the uncertainties in the model results, different scenarios and sensitivity analyses are undertaken. In these instances, the values of different inputs are varied to reflect the uncertainty in the estimate e.g., healthcare costs, health state values, and long-term survival predictions.

Additional considerations

NICE has introduced a tool called the severity modifier which NICE allows to increase the QALYs for drugs used to treat severe diseases.²⁸ This model increases the QALYs above by 1.7 times, reflecting the severe and life-limiting nature of advanced GIST.²⁸

The QALY calculation may not fully capture the QoL benefits associated with the use of ripretinib for patients with advanced GIST as the model does not capture the impact of ripretinib on caregivers' QoL.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Innovation

There are currently no approved treatments in the UK for patients with advanced GIST whose disease continues to progress or who cannot tolerate third-line regorafenib.⁶ This creates a significant unmet need, which ripretinib can help address.

Ripretinib is an innovative treatment offering clinicians and patients a new treatment option when other treatments become ineffective in the management of GIST. Ripretinib was developed for patients with advanced GIST for whom other TKIs have become ineffective meaning it may still inhibit cancer cell growth when other TKI treatments cannot.

Clinicians and patients agree on the innovative nature of ripretinib:

- Patient expert statement from NICE ID3805 (TA881)⁹: *“The opportunity to use ripretinib, a drug specifically designed to target the newly developed mutations and prolong life is amazing.”*
- Clinicians statement from NICE ID3805 (TA881)⁹: *“[Ripretinib] is a meaningful treatment option for patients with metastatic GIST in the 4th line setting who currently have no other treatment options and which is in my opinion an unmet need ... [ripertinib] is a significant ‘step change’, the first in 5 years since the licensing of regorafenib.”*

Benefits not captured in the model

The health economic analysis did not capture the potential effects of the burden of advanced GIST on caregivers. Similarly, the model did not capture any effect of death of the patient and bereavement on caregiver and family quality of life. Data to inform such analyses are not available but such effects are likely to exist. The ability of patients to maintain HRQoL whilst receiving ripretinib, including physical and role function, suggests a potential reduction in dependence on carers, thereby improving carers QoL.

The effect of having an additional line of therapy available after regorafenib on patient QoL was also not captured for the same reason. This would give patients hope that they can live a somewhat normal life for longer than currently possible. Hope is a factor that does not come into consideration in traditional drug appraisals.²⁹

3I) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues here

No equality issues were identified.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE

assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.

Information related to GIST:

- [GIST Cancer UK](#)
 - <https://gistcancer.org.uk/wp-content/uploads/publication-gist-for-beginners-2024.pdf>
- [Sarcoma UK](#)
- [PAWS GIST Clinic](#)
- [Cancer Research UK](#)

UK clinical guidelines:

- Gastrointestinal stromal tumour (GIST): British Sarcoma Group clinical practice guidelines 2024: <https://www.nature.com/articles/s41416-024-02672-0>
- UK clinical practice guidelines for the management of gastrointestinal stromal tumours (GIST) 2017: <https://clinicalsarcomaresearch.biomedcentral.com/articles/10.1186/s13569-017-0072-8>

Key published INVICTUS clinical trial data:

- Symcox M, Somaiah N. Ripretinib for advanced gastrointestinal stromal tumor: plain language summary of the INVICTUS study. *Future Oncology*. 2021;17(36):5007–5012. doi:10.2217/fon-2021-0803
- Blay J-Y, et al. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial. *The Lancet Oncology*. 2020;21(7):923-934. [https://doi.org/10.1016/s1470-2045\(20\)30168-6](https://doi.org/10.1016/s1470-2045(20)30168-6)
- Zalcborg J, et al. Clinical Benefit of Ripretinib Dose Escalation After Disease Progression in Advanced Gastrointestinal Stromal Tumor: An Analysis of the INVICTUS Study. *The Oncologist*. 2021;26(7):2053–2060. <https://doi.org/10.1002/onco.13917>
- Schöffski P, et al. 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*. 2022;22. <https://doi.org/10.1186/s12885-022-10379-9>

Related NICE guidance:

- Ripretinib for treating advanced gastrointestinal stromal tumour after 3 or more treatments: [Technology appraisal guidance | TA881 | Published: 03 May 2023](#)
- Regorafenib for previously treated unresectable or metastatic gastrointestinal stromal tumours: [Technology appraisal guidance | TA488 | Published: 15 November 2017](#)
- Sunitinib for the treatment of gastrointestinal stromal tumours: [Technology appraisal guidance | TA179 | Published: 23 September 2009](#)
- Imatinib for the treatment of unresectable and/or metastatic gastro-intestinal stromal tumours: [Technology appraisal guidance | TA86 | Published: 27 October 2004](#)

Further information:

- Public Involvement at NICE: [Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- NICE's guides and templates for patient involvement in HTAs: [Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector \(VCS\) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- EUPATI guidance on patient involvement in NICE: <https://www.eupati.eu/guidance-patient-involvement/>
- EFPIA – Working together with patient groups: <https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf>

- National Health Council Value Initiative: <https://nationalhealthcouncil.org/issue/value/>
- INAHTA: <http://www.inahta.org/>
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Adverse event (AE) – An undesired effect of a drug or other treatment. AEs can range from mild to life-threatening

Alopecia – Loss of hair from parts of the body where hair normally grows

Best supportive care (BSC) – Care that focuses on relieving symptoms and improving quality of life, rather than treating the cancer itself

Biopsy – Removing a small sample of tissue so a specialist can examine it under a microscope

Clinical trial – A research study in which people volunteer to test a new treatment to see how safe and effective it is

Double-blind study – A type of clinical trial in which neither the participants nor the study doctors know who is getting the new treatment or the comparison treatment until the study ends

EORTC QLQ-C30 – A questionnaire that asks people with cancer about their symptoms, daily activities and overall quality of life

EQ-5D-5L – A short questionnaire that measures general health in five areas

EQ-VAS – A 0-to-100 scale on which patients mark how good or bad their health feels that day

Gastrointestinal stromal tumour (GIST) – A rare cancer that starts in the digestive system, most often in the stomach or small intestine

Histologic confirmation – Laboratory examination of tissue (from a biopsy) to confirm exactly what type of cells are present

HRQoL (health-related quality of life) – How a person's health affects their everyday life and well-being

Imatinib – A medicine that blocks specific proteins inside cancer cells to slow or stop the growth of GIST; usually the first treatment given

INVICTUS – The name of the main clinical trial that tested ripretinib in people with advanced GIST

KIT – A gene, specifically, proto-oncogene c-KIT, that commonly becomes mutated in GIST

Metastatic – Describes cancer that has spread from where it started to other parts of the body

Molecular analysis – Lab tests that look for genetic changes (mutations) in tumour cells.

Mutation – Any change in a cell's DNA; some mutations help tumours grow

Objective response rate (ORR) – The percentage of patients whose tumours shrink or disappear after treatment

Overall survival (OS) – The length of time from diagnosis or start of treatment that patients are still alive

Palmar-plantar erythrodysesthesia (PPES) – Soreness, redness or blisters on the palms of the hands or soles of the feet; also called "hand-foot syndrome"

Patient-reported outcome (PRO) – Information patients give directly about their symptoms, feelings, or daily functioning

PDGFRA – A gene, specifically the platelet-derived growth factor receptor alpha gene, that commonly becomes mutated in GIST

Phase III – A late stage of clinical testing that compares a new treatment with the current standard or a placebo in a larger group of patients

Placebo – An inactive substance or other intervention that looks the same as, and is given the same way as, an active drug or treatment being tested. The effects of the active drug or other intervention are compared to the effects of the placebo.

Progression-free survival (PFS) – The length of time during and after treatment that the cancer does not grow or spread

Quality-adjusted life year (QALY) – A combined measure of quantity and quality of life; one QALY equals one year in perfect health

Regorafenib – A targeted treatment used after imatinib and sunitinib stop working

Ripretinib – A newer targeted treatment designed to work even when GIST has become resistant to earlier drugs

Sarcoma – A group of cancers that start in bone or soft tissues such as muscle, fat or blood vessels

Statistical significance – Evidence from a study showing the result is unlikely to have happened by chance

Sunitinib – A medicine given when imatinib no longer keeps GIST under control

Tyrosine kinase inhibitor (TKI) – A substance that blocks enzymes called tyrosine kinases, which help cancer cells grow; TKIs are a form of targeted therapy

Unresectable – A tumour that cannot be removed completely with surgery

4c) References

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments (review of TA881) [ID6496]

Clarification questions

June 2025

File name	Version	Contains confidential information	Date
ID6496 Ripretinib clarification letter response_redacted	V.1	No	30 June 2025

Section A: Clarification on effectiveness data

SLR for clinical evidence

A1. Company's submission (CS) Appendix B, Section 2, pages 34-50. With reference to the systematic literature review (SLR) of clinical effectiveness evidence, please provide details of the number of reviewers involved and the methods used for screening citations and full-text articles, extracting data, and assessing study quality.

Publications identified through the systematic review were evaluated in a three-step process to assess whether they should be included in data extraction. The inclusion/exclusion criteria used against the publications were developed using the (Population, Intervention, Comparison, Outcome, Study design) PICOS format (for inclusion/exclusion criteria see CS appendices, Appendix E, Table 9).¹ The search strategy is presented in CS Appendix B, Table 4, and details the points at which duplicates were removed from the search outputs. This procedure complies with stringent Health Technology Assessment (HTA) guidelines surrounding the methodology of systematic reviews.²⁻⁴

Title/abstract review

All publications were independently reviewed against the inclusion/exclusion criteria based on their abstract and title. All abstracts were screened by two independent reviewers, with a third party available to resolve discrepancies; all publications included by the reviewer at the end of this stage were retained for full-text review. For publications excluded at the abstract review stage, the reason for rejection was documented for use in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram according to the National Institute for Health and Care Excellence Decision Support Unit (NICE DSU) guidance.^{3,5}

All publications included in the title/abstract review are presented in the accompanying Excel SLR Report, with the title, source, authors, and abstract provided.⁶

Full-text review

Publications included after title/abstract review underwent full review of the text. A record was kept of publications excluded at this stage along with clear justification for their exclusion as per NICE DSU guidance.^{3,6} All publications excluded during full-text review are presented in the accompanying Excel SLR Report, tab “Clin FT Review”, with the title, source, authors, abstract and reason for rejection provided for review.⁶

Two independent reviewers screened all citations and full-text articles and any discrepancies in their decisions were resolved by a third independent reviewer.

Data extraction

Data from studies still included after full-text review were extracted into a pre-defined Microsoft Excel®-based template, ensuring that data were extracted uniformly and extraction was comparable for all studies. Two analysts independently extracted data, which were then checked and reconciled by a third independent analyst.

To ensure process consistency, researchers performing data extraction underwent specific training.² Additional follow-up was implemented to address any issues identified that related to data extraction.

Quality assessment

An assessment of quality was performed on abstracts, posters, or full-text articles of relevant Randomized Controlled Trials (RCTs) using the NICE checklist.⁷ Two reviewers independently ranked each included study and then discussed their quality assessments as required to resolve any disagreements.

A quality assessment was conducted for relevant RCTs published in four studies, comprising INVICTUS, VOYAGER, NCT02880020 and CHAPTER-GIST-301. Results of the quality assessment are presented in the SLR Excel Report, tab “QA RCT”.⁶

Full details of the methods used are presented in the SLR write-up report.¹

Clinical effectiveness evidence

A2. CS, Section 2.6.2, pages 54 to 55 and Figure 4. The text states that at the 10th August 2020 data cut-off (DCO), 65 patients in the ripretinib group had progressed, of whom 43 dose escalated to ripretinib 150mg twice daily (BID) and 22 patients either continued ripretinib 150mg Once daily (QD) or discontinued study treatment. Please clarify how many of the 22 patients continued ripretinib 150mg QD and how many discontinued.

Table 1 presents a breakdown of the treatment status of the 22 patients who either continued on ripretinib 150 mg QD or discontinued study treatment.

Table 1: Breakdown of patients who either continued on 105 mg QD post-progression or discontinued study treatment (n=22)

Actions for 22 patients that did not dose escalate	Frequency count
Continued onto 150 mg QD	16
Discontinued from the double-blind period	6

Abbreviations: QD = Once daily

A3. PRIORITY. CS, Section 2.6.2, page 54. The text states *“As of January 2021, 63 of the 85 patients originally randomised to ripretinib had entered the open label period following disease progression based on independent radiological review. Of those, 19 continued to receive 150 mg QD and 44 underwent Inter-patient Dose Escalation (IPDE) to 150 mg BID.”* Please provide information on the duration of post-progression ripretinib treatment at each dose (mean, standard deviation and range).

The duration of post-progression ripretinib treatment at each dose is presented in Table 2. The analysis set comprises patients randomised to ripretinib who underwent disease progression (N = 65).

The 63 patients cited in the question and in the text in Section 2.6.2 are described in the disposition table (referenced as Table 74 in the CS) which summarises the number of patients who moved into the open-label phase and the treatment they received.

The 65 patients described in Table 2 are strictly defined as patients who progressed according to the time to progression rules (TTP, in the statistical analysis plan [SAP])

and the treatment subsequently received. This aligns with other tables based on disease progression and the analysis approaches used within the submission. Four patients were censored in the TTP analysis but continued into the open-label phase later, so are not included in Table 2. Six patients progressed but did not enter the open-label phase and are included in Table 2.

Table 2: Duration of post-progression ripretinib treatment (weeks) (January 2021 data-cut off)

Ripretinib dose	Number of patients	Mean	SD	Minimum	Maximum
QD only					
QD before IPDE*					
BID					

Abbreviations: BID = 150 mg twice daily; IPDE = Inpatient dose escalation; QD = 150 mg once daily; SD = Standard deviation

*Represents the time between progression and patients starting BID treatment

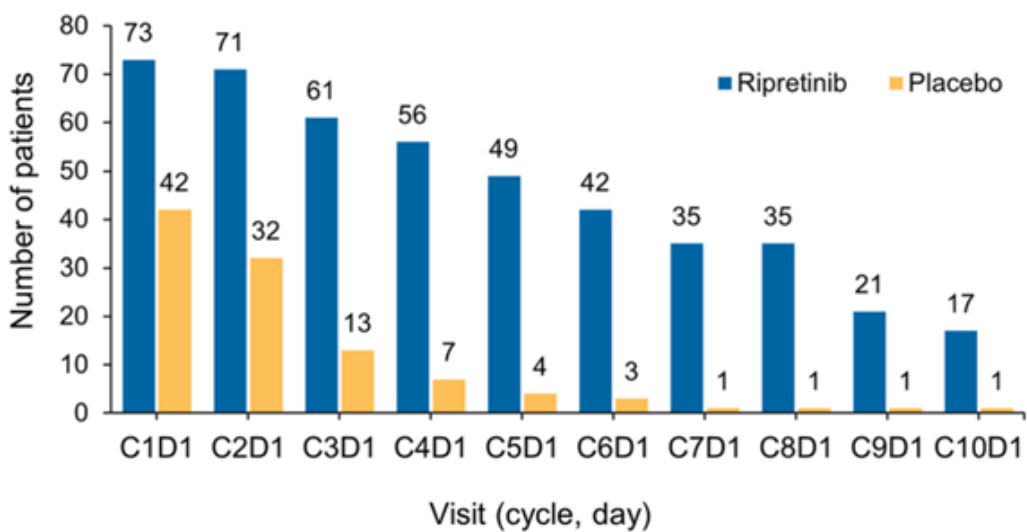
A4. CS, Section 2.62, page 75. The CS states that health-related quality of life (HRQoL) in INVICTUS was assessed using the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ C30) role and physical functioning domains, the Euroqol 5-Dimensions 5-Level (EQ-5D-5L) and the Euroqol Visual Analogue Scale (EQ VAS) from baseline to only Cycle 2 Day 1 and that this was due to the small number of patients after this time point. Please clarify why only a small number of patients were evaluated for HRQoL at later cycles.

The small number of patients evaluated for HRQoL at later cycles is particularly related to patients randomised to placebo. The number of patients in the placebo arm was low after Cycle 2 Day 1 due to rapid disease progression, meaning that any statistical comparison across study arms after this time point would be highly uncertain. Specifically, the patient-reported outcome (PRO) evaluable population in the placebo arm fell from 32 patients at Cycle 2 Day 1 to 13 patients at Cycle 3 Day 1 (Figure 1).^{8,9}

The rapid decline in the number of patients in the placebo arm was expected due to the severity of their fourth-line advanced gastrointestinal stromal tumour (GIST). As a result, comparative statistical analysis across study arms was only pre-specified up to Cycle 2 Day 1.¹⁰

Of the 84 patients who received ripretinib during the double-blind period, the PRO-evaluable population comprised 73 patients with an available baseline assessment. At Cycle 10 Day 1, 17 patients had PRO assessment, facilitating the analysis of longitudinal changes in PRO score from baseline in the ripretinib arm (Figure 1).⁸

Figure 1: Number of patients with PRO assessment over time in INVICTUS



Abbreviations: C = cycle; D = day; PRO = patient-reported outcome
Source: Schoffski et al., 2022⁸

A5. CS, Section 2.3.2, Table 8, page 38. Please provide a breakdown of the number of patients with an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 1 and the number of patients with an ECOG PS of 2 in INVICTUS.

Table 3 presents a breakdown of the number of patients with an ECOG PS of 1 and the number of patients with an ECOG PS of 2 in INVICTUS.¹¹

Table 3: ECOG scores at screening in the double-blind period (Intention-to-treat Population [ITT])

ECOG score at Screening	Ripretinib (N=85)	Placebo (N=44)	Total (N=129)
1			
2			

Abbreviations: ECOG = Eastern Cooperative Oncology Group
Source: INVICTUS Clinical Study Report¹¹

A6. PRIORITY. CS, Section 2.3.3, Table 8, page 38. Despite randomisation being stratified by ECOG PS in INVICTUS, the placebo group had slightly worse PS scores and older age. Please comment on the potential implications of this imbalance.

As a rare oncology indication, clinical trials in advanced GIST have relatively small patient populations, which makes stratifying patients by baseline parameters more difficult.¹²

Multiple sources agree that both age and ECOG PS are key prognostic factors for survival in advanced GIST, where lower ECOG PS score and a younger age favour longer survival.¹³⁻¹⁵ However, clinicians consider ECOG PS, the presence of secondary resistance mutations, and disease burden to be more important treatment effect modifiers than age.¹⁶

Subgroup analyses were conducted for progression-free survival (PFS) (prespecified), overall survival (OS) and overall response rate (ORR), to assess the impact of age, ECOG PS and other factors on the findings. Ripretinib showed benefit (hazard ratio [HR<1]) across all subgroups assessed. None of the subgroup analyses showed that age or ECOG PS had a statistically significant impact on ripretinib benefit (for PFS see CS Section 2.8.1 Figure 21, for ORR see CS Appendix C Figure 5, and for OS see INVICTUS Clinical study report, Figure 14.2.4.1, page 569).¹¹

Similar subgroup analyses as conducted for the pivotal trials considering tyrosine kinase inhibitor (TKI) use at earlier treatment lines for advanced GIST, were also investigated. In general, these trials also showed that age and ECOG PS were not statistically significant treatment effect modifiers (Table 4).^{17,18}

Table 4: Comparison of subgroup analysis considering different lines of TKI treatment for advanced GIST

	ECOG		Age	
	Overall survival	Progression-free survival	Overall survival	Progression-free survival
Ripretinib (INVICTUS)^{11,12}		Numerically superior HR for ECOG 1 or 2 vs ECOG 0 (95% CIs overlapping)		Numerically superior HR for older age (95% CIs overlapping)
Regorafenib (TA488)¹⁷	<i>Redacted</i>	Numerically superior HR for ECOG 0 vs ECOG 1 (95% CIs overlapping)	<i>Redacted</i>	Numerically superior HR for older age (95% CIs overlapping)
Sunitinib (TA179)¹⁸	Suggests ECOG 0-1 favours longer survival vs ECOG 2	Numerically superior HR for ECOG 0 vs ECOG 1 (95% CIs overlapping)	Suggests age <59 years favours longer survival vs age ≥59 years	Numerically superior HR for older age (95% CIs overlapping)

Abbreviations: CI = Confidence interval; ECOG = Eastern Cooperative Oncology Group; GIST = Gastrointestinal stromal tumour; HR = Hazard ratio; TKI = Tyrosine kinase inhibitor

Overall, considering the lack of statistical significance of subgroup analyses across trials and the relatively small magnitude of the imbalances between treatment arms, it is unlikely that the imbalances seen in INVICTUS had a meaningful impact on the clinical effectiveness results. Therefore, any differences should not affect the interpretation of ripretinib's relative benefit, especially given its magnitude (improvement in median PFS of 5.3 months and median OS of 11.9 months as of 15 January 2021).¹⁹

A7. CS, Section 2.8.1, Figure 21, page 88. The subgroup analysis of progression-free survival (PFS) in INVICTUS suggests that patients with ECOG PS 0 had a worse treatment effect of ripretinib compared to those with ECOG PS 1–2. Also, older patients appear to have a greater treatment effect. These results appear counterintuitive, please comment on these findings.

As previously mentioned, due to the rarity of $\geq 4^{\text{th}}$ line advanced GIST and therefore relatively small size of the INVICTUS trial, the subgroups analysed were small. The findings of the subgroup analysis suggest that ripretinib provides benefit across all subgroups; however, the subgroups analysed were not large enough to support any further conclusions.¹⁹

Additionally, subgroup analyses consider a single variable in isolation and there may be other imbalances in baseline characteristics between subgroups that drive these counterintuitive results, particularly given the small patient numbers in each subgroup. Therefore, we explored the baseline characteristics between the ECOG PS and age subgroups.

Interestingly, there was an imbalance between the ECOG PS and age subgroups in KIT exon 11 mutations for the ripretinib arm (Table 5). KIT exon 11 mutations are known treatment effect modifiers for TKIs in advanced GIST. Analysis of the UK compassionate use cohort showed that the presence of a primary KIT exon 11 mutation was consistently associated with significantly longer PFS, time-to-discontinuation (TTD) and OS.²⁰ This has also been demonstrated by subgroup analyses of the INTRIGUE trial, an open-label, phase 3 study in patients with second-line advanced GIST who were randomized to either ripretinib or sunitinib.²¹ The ongoing INSIGHT trial aims to further explore the favourable response to ripretinib in patients with primary KIT exon 11 and secondary KIT exon 17/18 mutations.²¹ In summary, being mindful of small numbers and limitations of this approach, the higher proportion of patients with KIT exon 11 mutations in the ECOG PS 1-2 and older subgroups vs the ECOG PS 0 and younger subgroup may have contributed to the counterintuitive results for the PFS subgroup analyses (Table 9).²²

Table 5: Frequency of baseline KIT exon 11 mutations across patient subgroups at randomisation (patients randomised to ripretinib)

Category	Ripretinib arm n (%)
Age subgroups	
18-64 years (n=57)	
≥65-74 years (n=20)	
75 years or older (n=8)	
ECOG PS subgroups	
0 (n=38)	
1-2 (n=47)	

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; KIT = Kit proto-oncogene; QD = Once daily

A8. CS, Section 2.3.4, pages 39-44. Please undertake a quality assessment of the Royal Marsden Expanded Access Cohort study using an appropriate tool given the study design.

The CASP Cohort Study Checklist for the Royal Marsden Expanded Access Cohort study is provided in a separate document.²³

A9. PRIORITY. CS, Section 2.3.4, Table 11, page 43 and Section 2.6.3, pages 82 to 86. Table 11 summarises the characteristics of the full real-world evidence (RWE) cohort, where 42% of the cohort received only two prior lines of treatment before ripretinib. If possible, please update Table 11 and Section 2.6.3 to reflect the subgroup with three prior lines of treatment, for a more appropriate comparison with the population relevant to this submission.

The requested analysis cannot be provided at this time, as the company does not hold relevant patient-level data for the Royal Marsden Study. This is due to the study being investigator led, and the study authors have not published or released the necessary data to update Table 11 and Section 2.6.3.

However, CS, Section 2.8.2, page 89, and Lim et al., 2024 discuss how in univariate and multivariate Cox regression models, the number of previous lines of treatment (2 vs 3 or more) was not associated with significant differences in PFS (QD or ITT) or OS.²⁰ This is consistent with the INVICTUS OS subgroup analyses of number of prior therapy lines (CS, Section 2.8.1, Table 18 and Figure 21).¹¹

Section B: Clarification on cost-effectiveness data

Survival analysis

B1. PRIORITY. CS, Section 3.3, pages 108-128. The data for TTD, PFS and OS used in the economic model reflect the January 2021 DCO of INVICTUS. Please clarify whether more recent data-cuts are available, and if so, why these have not been used.

There is a later data cut-off (DCO) from INVICTUS dated May 2022. However, preparation and analysis for the NICE submission began before the 2022 DCO analysis became available. Therefore, the original model was built using data from the 2021 DCO. When the May 2022 DCO became available, the feasibility and possible impact of the final OS data on cost-effectiveness was investigated.

Overall, the median OS for each treatment arm using the May 2022 DCO is the same as for the January 2021 DCO. The small difference in HR seen between the two sets of data could be explained by random variation, given the small sample size and/or prolonged OS seen for participants in the placebo arm who survived beyond the median OS which was primarily driven by treatment crossover. All patients randomised to placebo who continued into the open-label period (N=30) were receiving ripretinib during the January 2021 to May 2022 data collection period and many had dose escalated (N=16/30).

Though the results were similar, we consider the 2022 data cut to be less robust than that for 2021. Prespecified end of study analyses only included OS and safety. PFS and HRQoL data had already been finalised from a statistical perspective and so further formal analyses were not appropriate. As such, a model incorporating 2022 data would be heterogenous with regards to clinical inputs for PFS, composite TTD, OS and HRQoL.

In addition, use of the 2022 DCO would increase the risk of bias and confounding. Moving further into the post-unblinding, post-treatment switch/IPDE period increases the potential risk due to informative drop-out and other biases associated with data collection in the open-label setting.

As the January 2021 data were mature, with OS data out to 24 months, it was considered that there was no value in integrating the new potentially less robust data cut into the model.

A summary of data from the 2022 DCO for patient disposition is presented in Table 6 and Table 7, OS data are presented in Table 8 and the Kaplan-Meier plot for OS is presented in Figure 2.²⁴

Table 6: Patient disposition in the double-blind period (ITT Population, as of 11 May 2022)

Category	Ripretin ib 150 mg QD (N=85) n (%)	Placeb o (N=44) n (%)	Total (N=129) n (%)
Populations			
ITT population	■	■	■
Safety population	■	■	■
PP population	■	■	■
PK population	■	■	■
Entered open-label period ^a	■	■	■
Discontinued treatment ^a	■	■	■
Primary reason for treatment discontinuation^a			
Adverse event	■	■	■
Clinical progression	■	■	■
Death	■	■	■
Physician decision	■	■	■
Confirmed PD by investigator	■	■	■
Confirmed PD by IRR	■	■	■
Termination by sponsor	■	■	■
Withdrawal of consent (study)	■	■	■
Withdrawal of consent (treatment)	■	■	■
Other	■	■	■
Discontinued study ^b	■	■	■
Primary reason for study discontinuation^b			
Death	■	■	■
Termination by sponsor	■	■	■
Withdrawal of consent (study)	■	■	■

Abbreviations: ITT = Intention-to-Treat; n = number of participants in a category; N = sample size; PP = Per Protocol; PK = Pharmacokinetics

^a Denominators are based on the number of participants in the safety population.

^b Denominators for study discontinuation are based on the number of participants in the ITT population.

Note 1: In the ITT/PP population, participant groups are based on the treatment initially assigned; in the safety/PK population, participant groups are based on the treatment initially received.

Note 2: The ITT population is defined as all participants who signed informed consent and were randomised. The Safety population is defined as all participants who received at least one dose of study drug. One participant was randomised to placebo but was never treated; the rest of the participants in the ITT population (N=128) were treated with their originally assigned treatment. The PP population is defined as randomised participants who did not have important protocol deviations that were expected to compromise efficacy and/or safety assessments, including inclusion/exclusion criteria deviations, participant receiving the wrong treatment, participant receiving an incorrect dose, and participant receiving prohibited medications. The PK population was defined as all participants who received at least one dose of ripretinib and had at least one non-missing PK concentration in plasma reported for ripretinib or the active metabolite DP-5439.

Note 3: One participant who discontinued treatment due to other reasons cited as 'transitioned to commercial ripretinib'. Source: Deciphera Data on File INVICTUS 2022 DCO (2025)²⁴

Table 7: Patient disposition in the open-label period (Safety Population, as of 11 May 2022)

Category	OL: Ripretinib 150 mg QD (DB: Placebo) n (%)	OL: Ripretinib 150 mg QD (DB: Ripretinib) n (%)	Ripretinib 150 mg BID n (%)	Enter OL: Total n (%)
Discontinued treatment				
Primary reason for treatment discontinuation				
Adverse event				
Clinical progression				
Death				
Physician decision				
Confirmed PD by investigator				
Confirmed PD by IRR				
Termination by sponsor				
Withdrawal of consent (study)				
Withdrawal of consent (treatment)				
Other				
Discontinued study				
Primary reason for study discontinuation				
Death				
Lost to follow-up				
Termination by sponsor				
Withdrawal of consent (Study)				
Other				

Abbreviations: BID = twice daily; IPDE = intra-participant dose escalation; n = number of participants in a category; N = sample size; OL = open-label; QD = once daily

Note 1: This summary includes participants who entered the OL period and received ripretinib 150 mg QD and/or ripretinib 150 mg BID, based on two analysis subperiods (Prior to- or Post-IPDE to ripretinib 150 mg BID). 'Prior to IPDE' means the participant entered the OL period on 150 mg QD and was eligible for IPDE.

Note 2: Three participants discontinued treatment for other reasons: one participant was 'Off study drug for more than a cycle (28 Days)', one participant due to 'Subject started new cancer treatment', and one participant due to 'Need to change treatment'. Source: Deciphera Data on File INVICTUS 2022 DCO (2025)²⁴

Table 8: Overall survival (ITT Population, as of 11 May 2022)

Categories	Statistics	Ripretinib 150 mg QD (N=85)	Ripretinib 150 mg Q D vs Placebo	Placebo (N=44)
Number of patients with an event	n (%)		--	
Number of patients censored	n (%)		--	
Kaplan-Meier estimate of overall survival (weeks)	25th percentile (95% CI)			
	Median (95% CI)		--	
	75 th percentile (95% CI)		--	
Log-rank test	p-value ^a	--		--
Cox proportional regression model	Hazard ratio	--		--
	95% CI ^c	--		--
Overall survival rate				
26 weeks	% (95% CI)		--	
39 weeks	% (95% CI)		--	
52 weeks	% (95% CI)		--	
78 weeks	% (95% CI)		--	
104 weeks	% (95% CI)		--	

Abbreviations: CI = confidence interval; ITT = intention-to-treat; n = number of participants in a category; N = sample size; NE = not estimable

^a p-value is based on a two-sided stratified log-rank test.

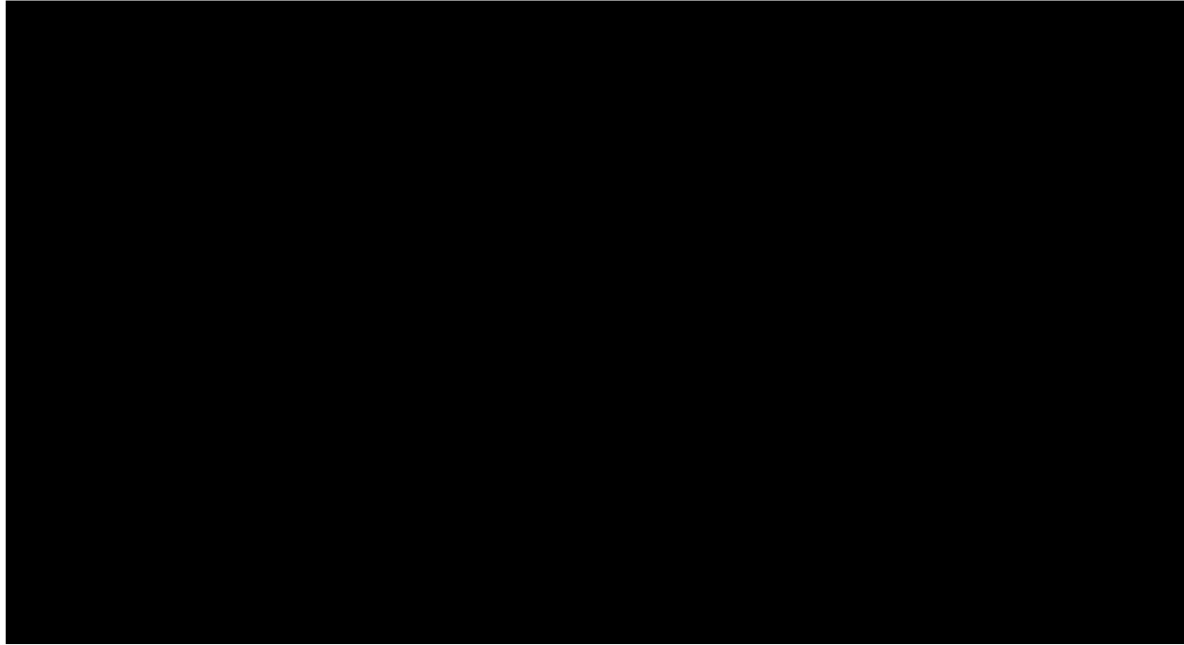
^b Cox regression model includes treatment and randomisation as fixed stratification factors.

° 95% CI based on Wald Method.

Note 1: Overall survival is defined as the time interval between the date of randomisation until the date of death or censored at the date of last follow-up.

Note 2: Participant groups are based on the treatment initially assigned. Source: Deciphera Data on File INVICTUS 2022 DCO (2025)²⁴

Figure 2: Kaplan-Meier plot of overall survival (ITT Population, as of 11 May 2022)



Abbreviations: CI = confidence interval; ITT = intention-to-treat; OS = overall survival; QD = once daily.
Source: Deciphera Data on File INVICTUS 2022 DCO (2025)²⁴

B2. PRIORITY. CS, Section 3.3.3, page 127. Time to treatment discontinuation (TTD) is modelled as a composite endpoint including treatment discontinuation on either QD or BID dosing and disease progression as events.

- (a) Please include further details about how the composite endpoint of PFS+TTD was calculated, including details of what was counted as an event and how censoring rules were applied.***
- (b) Please clarify why it was necessary to include PFS in the composite endpoint – why was time to treatment discontinuation not instead analysed as the time from study entry through to discontinuation on the last received dose of ripretinib in either the double-blind or open-label periods of INVICTUS?***
- (c) Section 2.4.1 on page 47 of the CS describes a post hoc TTD analysis, including any dose discontinuation during both the double-blind and***

open-label periods. The TTD definitions and calculations appear inconsistent between Sections 2.4.1 and 3.3.3. Why was the analysis in Section 2.4.1 not used as the base case? If these are separate analyses, please clarify the differences and explain which estimates were used in the model.

(a) TTD was considered a composite endpoint, when it was combined with PFS and treatment discontinuation into a single outcome, calculated as follows:

1. Time from randomisation to a composite endpoint of PFS plus treatment discontinuation (QD or BD) over the double blind (DB) and open-label (OL) periods.
2. The event time was measured from the date of randomisation to the latest of PFS and treatment discontinuation, calculated in weeks. Due to the PFS censoring rules pertaining to two or more missing assessments (refer to INVICTUS SAP)¹⁰, patients who:
 - a. [did not either discontinue treatment, and/or
 - b. who were considered as censored for PFS], and
 - c. who died

were assumed to have had the composite endpoint event at the time of their death.

3. Patients without the above composite event (i.e. as described in step 2 above) were considered as censored.
4. The censoring time was measured from date of randomisation to the latest of the two component times (PFS or last treatment), regardless of the event/censoring of each component.

Randomisation was chosen as the start date in order to align with calculation of time to PFS and OS as defined for analyses described in the clinical study report.

No subjects had missing TTD data.

(b and c) PFS was included in the composite TTD endpoint because the economic model uses four partitions, explicitly separating progressed patients who remain on ripretinib from those who progressed but discontinued ripretinib. This approach was adopted to specifically address the effects of post-progression ripretinib use, in response to committee and ERG feedback on the proposed stopping rule in TA881 and to ensure the model reflected UK clinical practice.^{16,25} An analysis based exclusively on TTD (as presented in section 2.4.1) would stratify all patients into either on- or off-treatment partitions regardless of progression status and would not correctly distinguish between PD-on-treatment and PD-off-treatment states; this was considered particularly important for capturing the effect of post-progression treatment on quality of life. Incorporating PFS into the composite ensures the model allocates patients to the appropriate post-progression partition.

B3. PRIORITY. CS, Section 2.6.2, Figure 10, page 65. For non-escalating patients in INVICTUS, the EAG understands that they either remained on ripretinib 150mg QD post-progression or received no further treatment and that the survival of these patients is calculated from the start of the trial. For those who escalated to ripretinib 150mg BID, survival appears to be measured from the first BID dose post-progression. Such comparisons are based on survival from different baselines (time of study entry and time of progression, respectively). This likely leads to immortal time bias, which cannot be corrected through statistical methods alone. Please clarify the following:

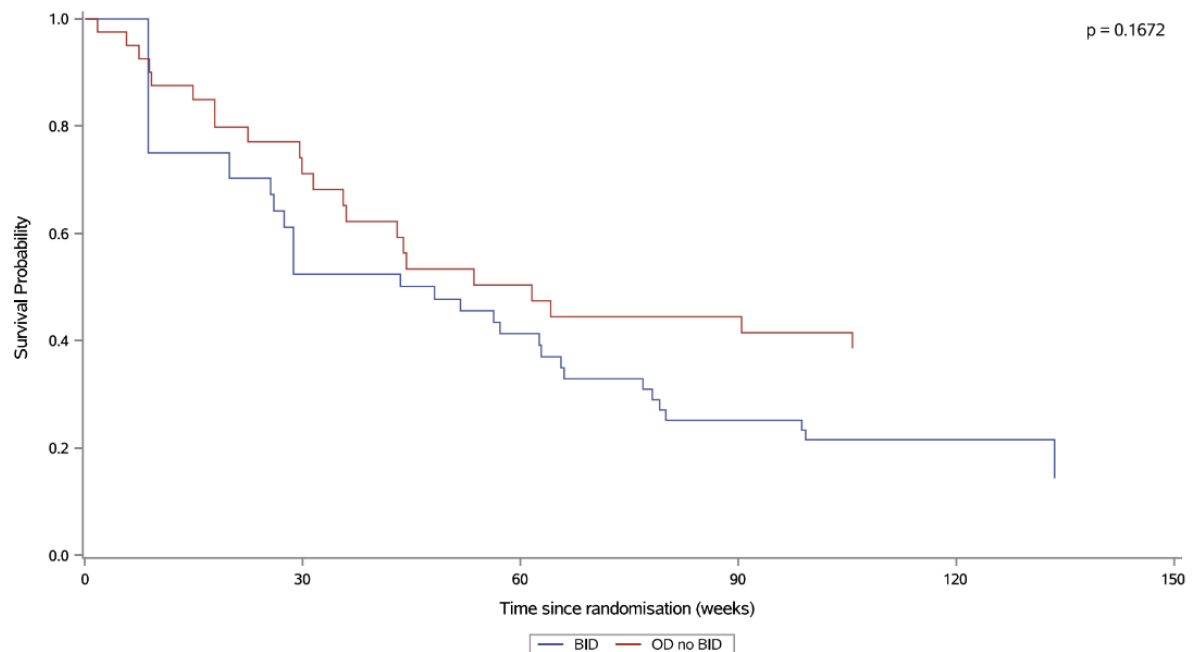
- (a) Is this analysis limited to patients randomised to the ripretinib treatment arm?*
- (b) Given the risk of immortal time bias, how should this analysis be interpreted?*
- (c) Please perform an updated analysis of post-progression survival from the first QD vs. BID dose among patients in the ripretinib arm after progression (assuming similar time from progression to next treatment in both cases), and report patient characteristics at the secondary baseline for the naïve comparison (at a minimum, report the covariates at secondary baseline used in the two-stage IPDE adjustment, including:*

time to progression, ECOG performance status at progression, EQ-5D VAS score at progression, and age at baseline), if feasible.

(a) Yes, the analysis is limited to patients who were randomised to the ripretinib treatment arm in INVICTUS.

(b) We acknowledge the risk of immortal time bias in CS, Figure 10. Figure 3 presents Kaplan-Meier estimates of time from study randomisation to death, incorporating left truncation in the ripretinib 150 mg BID arm. Patients in this treatment arm, therefore, have delayed entry into the OS risk set. This analysis was conducted to account for the differing time origins between treatment dose groups, specifically addressing the risk of immortal time bias in the escalating (BID) population, although the presence of any treatment selection bias has not been adjusted for in Figure 3. The analysis incorporates the time post randomisation that patients started BID treatment, so they are not considered in the risk set prior to that time. Compared with the original analysis, patients who dose escalated had a slightly poorer survival probability compared with those who remained on the same dose, but this was not statistically significant. As such, this data adds to the other analyses included in CS, Section 2.6.2, page 63, by demonstrating the uncertainty surrounding the impact of ripretinib dose escalation on OS in INVICTUS given the considerable variability in the magnitude of and the positive/negative nature of the effect.

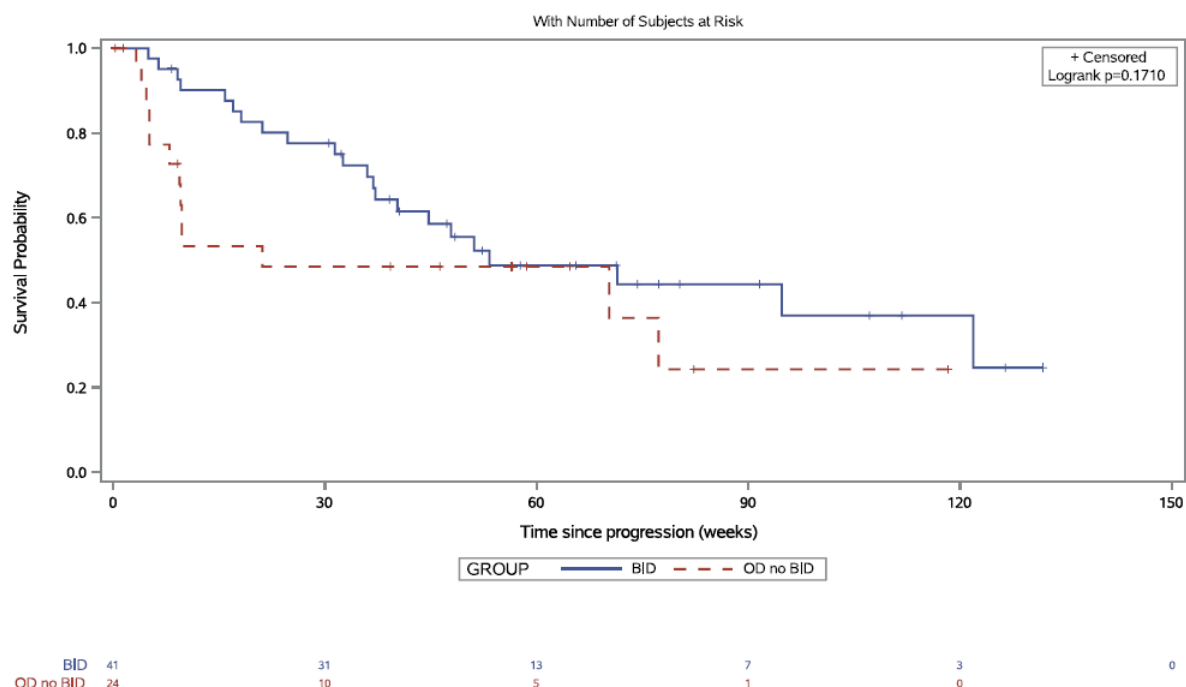
Figure 3: Kaplan-Meier plot of time from randomisation to death, patients randomised to ripretinib, allowing for left truncation of BID onset



Abbreviations: BID = Twice daily; OD = Once daily

(c) Figure 4 shows post-progression survival in patients randomised to ripretinib for those who remained on QD dosing versus those patients who underwent IPDE. Initially, there was a survival advantage for patients who dose escalated versus those who remained on QD dosing; however, the curves converged at around 50 weeks post-progression. This initial benefit was likely to be due to imbalances in positive prognostic factors across the two populations since randomisation was broken at disease progression.

Figure 4: Kaplan-Meier plot of time from disease progression to death, for patients randomised to ripretinib at the time of disease progression



Abbreviations: BID = Twice daily; OD = Once daily

Table 9 presents a summary of patient demographic data and disease status, comparing patients who continued with 150 mg QD dosing vs those who dose -escalated to 150 mg BID. The data suggest that those who underwent IPDE were generally fitter and better able to tolerate dose escalation. Patients who continued with QD dosing were more likely to have ECOG PS ≥ 1 at baseline (62.5% vs 53.7% who dose escalated to BID) and were more likely to have ≥ 4 prior lines of therapy (41.7% for QD vs 31.7% for BID). This was also seen at the point of progression, where a much lower proportion of patients who stayed on QD post progression had ECOG score of 0 (16.7%) compared with those who dose escalated to BID (51.2%). Patients who dose escalated also had a better Euroqol Visual Analogue Scale (EQ-5D VAS) score at the point of progression vs those who did not dose escalate (Table 9).²²

Table 9: Summary of patient demographic and disease status at progression where the analysis set is patients randomised to ripretinib with progression (N = 65)

	Ripretinib 150 mg QD (n=24)	Ripretinib 150 mg BID (n=41)
Age at baseline	57.4 (10.6%)	60.0 (10.8%)
Sex		
Male	13 (54.2%)	23 (56.1%)
Female	11 (45.8%)	18 (43.9%)
Race		
White	15 (62.5%)	33 (80.5%)
Non white	9 (37.5%)	8 (19.5%)
Region		
USA	11 (45.8%)	15 (36.6%)
Non USA	13 (54.2%)	26 (63.4%)
Number of previous therapies stratification		
3	14 (58.3%)	28 (68.3%)
≥4	10 (41.7%)	13 (31.7%)
ECOG PS stratification at screening		
0	9 (37.5%)	19 (46.3%)
1 or 2	15 (62.5%)	22 (53.7%)
ECOG PS*		
0	4 (16.7%)	21 (51.2%)
1	16 (66.7%)	15 (36.6%)
2	2 (8.3%)	5 (12.2%)
3	2 (8.3%)	0 (0%)
EQ-5D VAS*	54.4 (21.1)	75.0 (17.3)
Tumour mutation gene		
KIT exon 9	3 (12.5%)	7 (17.1%)
KIT exon 11	13 (54.2%)	25 (61.0%)
Other KIT	8 (33.3%)	9 (22.0%)

Abbreviations: CfB = Change from Baseline; NA = Not applicable; N = Number of patients with post progression treatment

Patients who switched dose in the absence of disease progression were excluded.

One patient had missing EQ-5D VAS at progression in the DCC-2618 150 mg BID group.

Mean (SD) displayed for continuous variables. N (%) displayed for categorical variables.

* Taken at time of progression

Source: Deciphera Data on File ²²

A UK clinical advisory board supported these findings, with clinicians stating that patients who did not dose escalate were more likely to be of ECOG PS ≥1 at the point of progression.¹⁶ ECOG PS was also identified as a key prognostic factor / treatment effect modifier; it was perceived that a difference in performance status could account

for a difference in OS between the two patient groups.¹⁶ Higher ECOG PS for those not dose escalating is likely to explain the rapid decline over the ~10 weeks post-progression for patients who remained on QD dosing; after 10 weeks the rate of decline plateaued for these patients over the long-term.

Eventual plateauing of survival curves aligns with comments by the advisory board that patients that reach the end of the survival curve probably have biologically better disease that would progress slowly whether on QD or BID dosing.¹⁶ Additionally, as stated in the response to B12, depending on the commissioning route for BID, only a select few patients would likely dose escalate to 150 mg BID in clinical practice. Therefore, any potential bias seen in the analysis is unlikely to be relevant to real world practice.

B4. PRIORITY. CS, Section 2.6.2, pages 63 to 72. Please clarify whether all *post hoc* OS analyses aimed at quantifying the IPDE effect were designed to weight or adjust patients who received ripretinib 150mg BID post-progression (44 patients as of January 2021) as if they had received 150mg QD. If not, please clarify the estimand for each analysis.

Table 10 describes the estimands for all post hoc analyses that were done to quantify the impact of IPDE to 150 mg BID.

Table 10: Estimands for all post hoc OS analyses aimed at quantifying the impact of IPDE

Analysis	Population	Intervention	Comparator	Outcome	Analysis method	Summary measure	Intercurrent events (ICs)	Handling of ICs	Dossier location
Open label BID vs QD OS analysis - #1	Full Analysis Set 2020 DCO	Ripretinib BID - only patients who switched	Ripretinib QD excluding patients receiving BID tx	Time from randomisation to death/ censoring	Kaplan-Meier estimates	N/A	Study-drop out/data cut	Patients censored at last known alive date	CS Section 2.6.2 Figure 9, page 64
Open label BID vs QD OS analysis - alternative	FAS patients randomised to ripretinib OD 2021 DCO	Ripretinib BID (post progression)	Ripretinib QD excluding patients receiving BID tx	Time from first dose (QD/BID) to death/ censoring	Kaplan-Meier estimates	N/A	Study-drop out/data cut	Patients censored at last known alive date	CS Section 2.6.2 Figure 10, page 65
BID censoring analysis - #1	Full Analysis Set 2021 DCO	Ripretinib QD including time on BID tx	Ripretinib QD excluding time on BID tx	Time from randomisation to death/ censoring	Kaplan-Meier estimates	N/A	Study-drop out/data cut, switch to BID	Patients censored at last known alive date or BID switch	CS Section 2.6.2 Figure 11, page 66
BID censoring analysis - #2	Full Analysis Set 2021 DCO	Ripretinib BID	Ripretinib QD	Time from randomisation to death/ censoring	Kaplan-Meier estimates	N/A	Study-drop out/data cut, progression	Patients censored at last known alive date or progression	CS Section 2.6.2 Figure 12, page 68
Cox proportional hazards time-varying analysis	Full Analysis Set 2021 DCO	Ripretinib BID	Ripretinib QD	Time from randomisation to death/ censoring	Cox time-varying regression	Hazard ratio (BID vs QD)	Study-drop out/data cut	Patients censored at last known alive date	CS Section 2.6.2 Page 68

Analysis	Population	Intervention	Comparator	Outcome	Analysis method	Summary measure	Intercurrent events (ICs)	Handling of ICs	Dossier location
Two-stage adjustment - Stage 1	FAS patients randomised to ripretinib QD 2021 DCO	Ripretinib BID	Ripretinib QD	Time from progression to death/ censoring	Parametric survival modelling	Acceleration factors & time ratios	Study-drop out/data cut	Patients censored at last known alive date	CS Section 2.6.2 Page 69

Abbreviations: BID = Twice daily; DCO = Data cut off; FAS = Full analysis set; ICs = Incurrent events; IPDE = Inpatient dose escalation; QD = Once daily; tx = Treatment

B5. PRIORITY. CS, Section 2.6.2, pages 63 to 72. Given that 97% of patients (63/65) who progressed received continued ripretinib (i.e., much higher than the 80% suggested by the clinicians consulted by the company), please also clarify whether post-progression QD ripretinib would alter the shape of the survival curve compared to those who received no further treatment.

Clinicians at the 2025 advisory board estimated that 80% of patients who initiate treatment with ripretinib would be likely to continue to receive ripretinib after disease progression.²⁶ The 97% quoted in the question, is the proportion of patients with disease progression who continued treatment beyond progression rather than the proportion of those who initiated treatment.

In INVICTUS, the proportion of patients who initiated treatment with ripretinib and continued treatment after disease progression was 74% (63/85), slightly lower than would be expected in clinical practice.²⁷ As such, the survival curves are likely to reflect what would occur in clinical practice.

B6. PRIORITY. CS, Section 2.6.2, Figure 12, page 68. Is the analysis illustrated in Figure 12 related to the analysis described on page 122 of the CS (“Censored BID-dosing analysis”)? If not, please clarify how the analyses differ from one another and explain which analysis is included in the scenario analyses in CS Table 60.

Yes, these analyses are the same. CS Figure 12 presents the survival curves to which the parametric models were fitted (p122). The results of this were then included as 2 scenarios in the model ‘Open label BID vs QD OS analysis (non-progressors + IPDE progressors; log logistic)’ and ‘Open label BID vs QD OS analysis (non-progressors + QD progressors; log logistic)’.

B7. PRIORITY. CS, Section 2.6.2, page 68. Please clarify whether the Cox proportional hazards time-varying analysis for ripretinib 150mg QD includes only the QD period after progression. If not, please explain what data were included in the analysis (including any reprocessing of those data).

The Cox proportional hazards time-varying analysis includes ripretinib 150 mg QD treatment (and any subsequent ripretinib 150 mg BID treatment) from randomisation

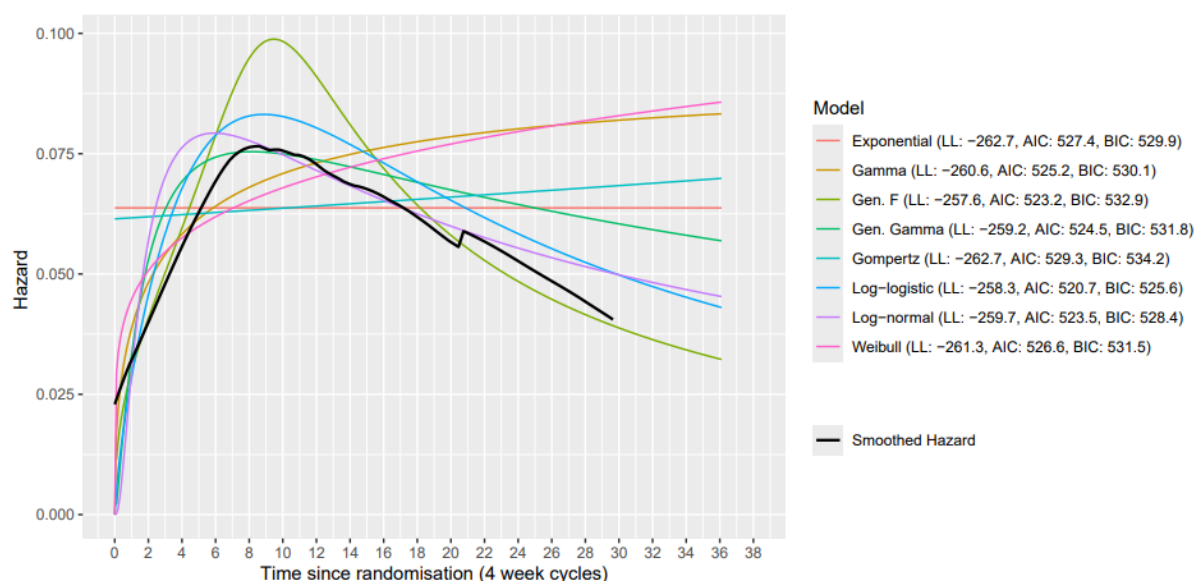
(rather than progression) until death/censoring (last known alive). The time from randomisation to death/censoring was split into periods (via a counting process which factored in changes in patient progression status, other time-varying variables, and treatment switch) giving start and stop times on ripretinib QD and ripretinib BID between randomisation, the date of escalation to ripretinib BID and death as appropriate. For example, for patients who dose-escalated from ripretinib QD to ripretinib BID, the assigned ripretinib QD period ended one day prior to the date of dose-escalation to ripretinib BID. The assigned ripretinib BID period, for the same patients, started on the date of the first ripretinib BID dose and ended at the date of death/censoring.

A small error in the allocation of death during these periods was identified, in which 13 patients were assigned a death event in multiple periods; this error was corrected. Updated comparison of ripretinib BID vs QD resulted in a HR of 1.50 (95% confidence interval [CI] 0.70 - to 3.22; $p=0.300$) indicating a 50% increase in the risk of death after dose escalation. This did not affect interpretation of the analysis.

B8. PRIORITY. CS, Appendix J, Figure 11, page 109. Please update the hazard plot for the composite endpoint of PFS+TTD to include the empirical smoothed hazard.

An updated hazard plot for the composite endpoint of PFS+TTD with the empirical smoothed hazard is presented in Figure 5.

Figure 5: Empirical hazard for the composite of PFS and discontinuation of ripretinib (any dose) with smoothed hazard

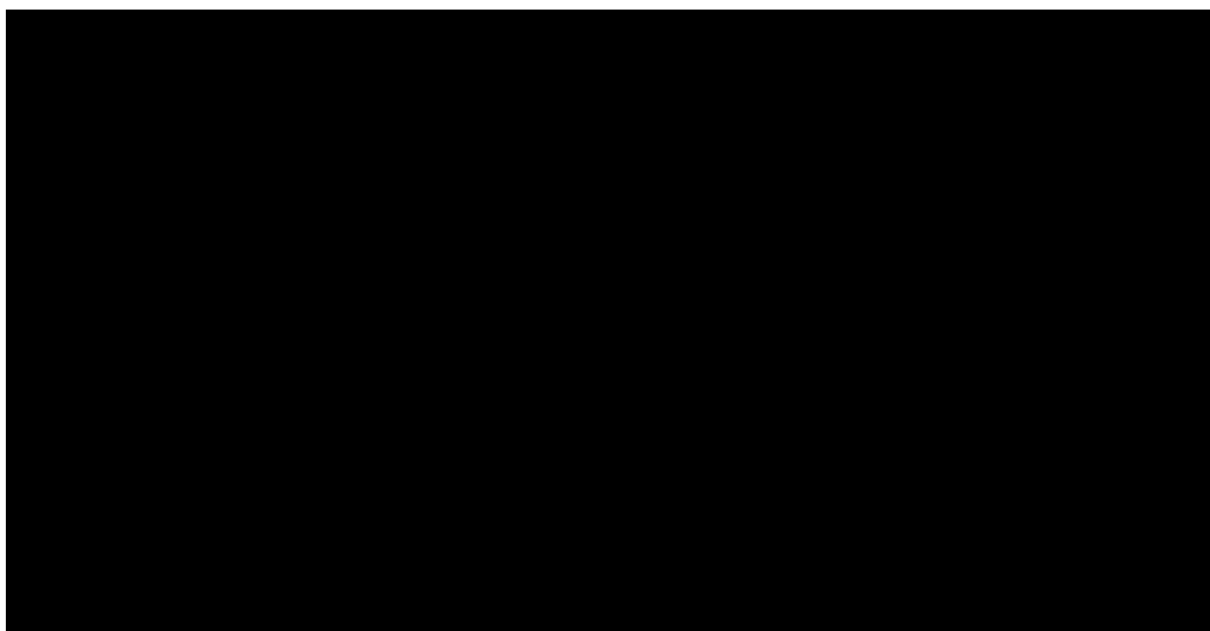


Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; LL = Log-likelihood

This plot is slightly different to that in Appendix J, Figure 11, page 109, which was the hazard plot for the time to discontinuation of ripretinib rather than the composite endpoint.

While generating this response it was noticed that CS Figure 32 and Table 37 present results for the TTD endpoint rather than the composite PFS+TTD endpoint. Figure 6 shows the correct plot for CS Figure 32 and Table 11 shows the correct data for CS Table 37.

Figure 6: Time to the composite of PFS and discontinuation of ripretinib (any dose)



Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; LL = Log-likelihood

Table 11: AIC and BIC statistical goodness of fit data for time to the composite of PFS and discontinuation of ripretinib

Distribution	Ripretinib	
	AIC	BIC
Exponential	527.4	529.9
Gamma	525.2	530.1
Weibull	526.6	531.5
Gompertz	529.3	534.2
Log-logistic	520.7	525.6
Lognormal	523.5	528.4
Generalised gamma	524.5	531.8

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; PFS = Progression-free survival

B9. PRIORITY. CS, Section 3.3.2, Table 36, page 124. With respect to the two-stage adjustment to account for the IPDE effect on OS in Table 36, please provide results from the Gompertz model for simple and complex adjustment models, and provide the following for all models:

- (a) Overlays of the different parametric survival models with the Kaplan-Meier estimates, for both the simple and complex adjustment models.*
- (b) Empirical hazard ratios of these models.*
- (c) Plots showing the empirical unsmoothed hazard, empirical smoothed hazard and modelled hazards.*
- (d) An explanation of the interpretation of survival time ratio estimates presented in this table.*
- (e) Please explain why the company did not instead first adjust the OS data and then fit parametric models to those adjusted data (as was done for the placebo group switching adjustment). Please conduct this analysis in a way which is consistent with the placebo group switching adjustment using the 2 stage estimation method.*

An extension for this response has been confirmed with NICE. The company clarification response for B9 will be submitted by 5 pm on 7 July 2025.

B10. PRIORITY. CS, Section 3.3.2, Table 34, page 122. Within the censored BID-dosing analysis, OS is assessed in two sub-populations based on post-progression treatment (IPDE vs. QD). Since this comparison is non-randomised and the groups differ in size, there is a risk of selection bias. Please comment on the potential impact of this selection bias on the interpretation of OS results.

Although the censored BID -dosing analysis can introduce selection bias due to informative censoring and loss of data over time, it is still thought to be of value as a comparison with other approaches that attempt to adjust the data for selection bias.

The imbalance of ECOG PS between those who escalated vs those who did not is likely to be a major factor that introduces uncertainty. Clinicians and multiple research papers indicate ECOG PS as a key prognostic factor for survival and a treatment effect modifier in patients with GIST.¹³⁻¹⁶ At the time of disease progression, patients

undergoing ripretinib IPDE had a better ECOG PS score than those not undergoing dose escalation (ECOG PS 0, 51% vs. 18%, respectively).²⁸ This aligns with clinician opinion, that expected patients who continued with ripretinib QD at the point of progression to be less fit or experiencing poor treatment tolerability.¹⁶ This suggests potential for selection bias in favor of BID dosing. Other unknown confounding factors are likely to exist as demonstrated by the variable results from the multiple analyses that aimed to quantify the effect of BID dosing while adjusting for potentially confounding variables (CS, Section 2.6.2, page 63).

Though there is a likelihood of selection bias, primarily due to the imbalance in ECOG PS at the point of progression, this scenario avoids introduction of other uncertainties resulting from attempts to adjust for this bias. Additionally, adjusted scenarios are presented in the form of the two-stage analysis and Cox proportional hazards time-varying analysis.

B11. PRIORITY. CS, Section 3.3.2, page 121. The CS states “Beyond the goodness of fit statistics, the loglogistic model extrapolation predicts that 8.6% of patients in the ripretinib arm would be alive at 10 years, which is in line with the upper end of estimates stated at a clinical advisory board held in July 2024.” However, the minutes of the 2024 advisory board meeting state [REDACTED]

[REDACTED] Please provide further justification for the selection of the log-logistic OS model.

Several steps were taken during selection of the OS model for ripretinib, in line with NICE DSU Technical Support Document 14. The resulting choice was a balance of the different factors considered. Firstly, independent parametric curves fitted the data and produced good visual predictions for ripretinib and best supportive care (BSC) within the observed period. Combined Akaike Information Criterion (AICs) and Bayesian Information Criterion (BICs) were calculated across treatment arms, yielding total values that were very closely matched for the best performing models and did not, therefore, meaningfully differentiate between models in terms of statistical fit. However, the fitted curves clustered into two groups in terms of estimated 10-year survival; whilst the Weibull and exponential curves estimated a 10-year survival of 1

to 2%, the other curves (log-logistic, log-normal, Gompertz and generalised gamma) all predicted a higher 10-year survival of around 8%.

We subsequently reviewed published data and sought expert opinion to validate whether 10-year survival with ripretinib was more likely to be aligned with the lower or higher curves:

- The 10-year survival rate for patients with advanced GIST who initiated previous lines of therapy is 10 to 23%.^{13-15,29} In patients treated with second-line sunitinib, 10-year survival was approximately 10%.²⁹ Patients typically progress quickly on sunitinib and regorafenib, with each line of therapy providing only 6 to 9 months of benefit.³⁰⁻³² As such, if the survival rate for patients treated with second-line sunitinib has been observed at 10% by 10 years then 10% at 9 years for ripretinib (as modelled in the base case) would be plausible.²⁹
- Clinicians (N = 7) in an advisory board were asked to estimate 10-year survival for ripretinib; however, responses were not aligned. One advisor commented that 8% survival at 10 years is plausible as treatments are improving and new options are being developed. Another thought that 10% at 10 years would be an over estimation. Four advisors provided estimates after the meeting of 1%, 2%, 2.5% and ≤5%.¹⁶
- Previous NICE TAs for advanced GIST indicate that clinicians repeatedly underestimate long-term survival associated with TKI treatment:
 - Imatinib: During the NICE appraisal [TA86] the Committee concluded that cost-effectiveness estimates based on a 10-year time horizon were sufficient to encompass key costs and benefits suggesting that no patients would remain alive at this timepoint. However, recent observational studies show PFS rates of nearly 10% at 10 years for first-line patients with advanced GIST treated with imatinib.³³
 - Sunitinib: For TA179 clinical experts estimated 10% survival at 6 years. However, a recent study has shown that median OS for second-line

treatment with sunitinib is 63.4 months (i.e. 50% of patients are alive at 5.3 years) with ~10% of patients surviving to 10 years.¹⁸

- A naïve comparison of clinical data for other TKIs used to treat advanced GIST vs ripretinib show that, although ripretinib is used in more heavily pre-treated patients who are more likely to harbour secondary drug-resistance mutations, it provides a higher magnitude of benefit than previous lines of therapy (Table 12). This is likely to be due to its novel ‘switch-control’ mechanism of action.

Table 12: Pivotal trial outcomes for treatments indicated for advanced GIST

Drug	ORR (%)	PFS (months)	OS (months)
Sunitinib (trial comparator) ³²	6.8 (0)	5.6 (1.5)	17.0 (14.9)
Regorafenib (trial comparator) ^{17,30,31,34}	4.5 (1.5)	4.8 (0.9)	17.4 (11.9)
Ripretinib (trial comparator) ^{12,19}	9.4 (0)	6.3 (1.0)	18.2 (6.3)

Abbreviations: ORR = overall response rate; OS = overall survival; PFS = progression-free survival

Considering these real-world 10-year survival estimates for advanced GIST with earlier lines of therapy, coupled with the higher magnitude of benefit ripretinib provides vs other TKIs and the uncertainty surrounding clinical predictions, it was decided that 1-2% survival at 10 years was too low and that 8% survival at 10 years was plausible as modelled by log-logistic extrapolation.

B12. PRIORITY. CS, Section 3.7, page 149. The base case model uses the unadjusted OS data from INVICTUS and assumes that the outcomes observed in the trial can be achieved using QD dosing (i.e., without escalation to BID dosing). This introduces an inconsistency between the what happened in the trial and the costs applied in the model. Please explain why the model scenario “Cost of ripretinib BID captured in 50% of patients remaining on treatment after progression” in CS Table 16 was not applied in the base case?

This scenario has not been applied in the base case for two main reasons:

1. It reflects off-license use of ripretinib and we understand that NICE can only issue guidance within the marketing authorisation.

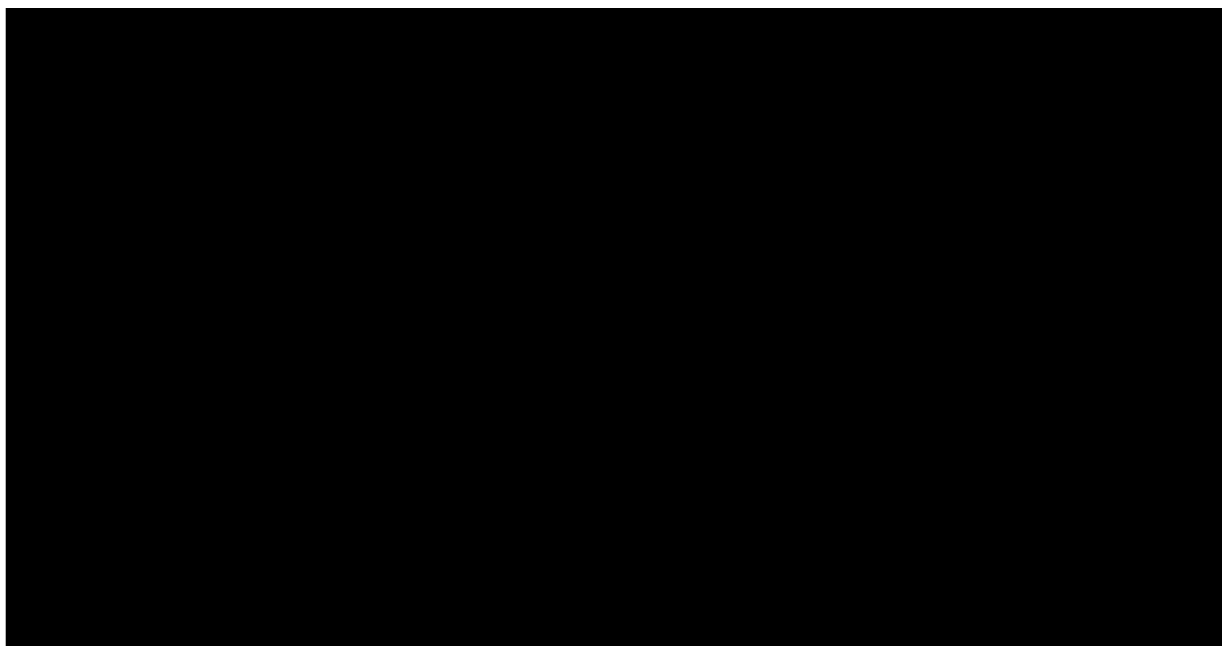
2. Deciphera is unclear as to how BID dosing would be commissioned within the NHS, and whether it being off-license would represent a barrier to its use. Deciphera sought clarity regarding this point from NHS England in June 2025 but has yet to receive a response. If ripretinib BID dosing were to be commissioned via individual funding requests for example, its use in clinical practice is likely to be far lower than that captured in the model scenario. Given this, we consider there is too much uncertainty on this point for the scenario to be considered in the base case.

Nevertheless, this scenario has been run and provided in Table 21 below.

B13. PRIORITY. CS, Section 3.3.3, Figure 32, page 127. Please provide the summary Kaplan-Meier estimates (in the same format as those provided in the executable model, worksheet “KM Data”) for the composite outcome of PFS+TTD which is used in the economic model.

The Kaplan-Meier data for the composite PFS+TTD outcome has been incorporated into the “KM Data” worksheet and a data series has been added to the chart on the “Clinical Inputs” worksheet, as illustrated in Figure 7.

Figure 7: Kaplan-Meier data for the composite PFS+TTD outcome



Abbreviations: KM = Kaplan Meier; PFS = progression-free survival; TTD = Time-to-discontinuation

Health-related quality of life (HRQoL)

B14. PRIORITY. CS, Section 3.4.5, pages 134 to 136. With respect to the mixed model for repeated measures (MMRM) analysis of the utility data in INVICTUS:

- ***Please clarify how switching in the control arm and dose escalation in the treatment arm were handled in the analysis of utilities for progressed disease (PD) for, BSC, PD on treatment, and PD off treatment?***
- ***Please also provide the full model specification of the MMRM (ideally as a formula) and report the relevant coefficients.***
- ***Please justify the preferred MMRM regression model specification, particularly the selection of regression covariates and how the model fit was assessed.***
- ***Please clarify the number of data points available for progression-free (PF), PD (BSC), PD on treatment and PD off treatment to inform the MMRM analysis.***

a) Subjects could transition from one state to another, across potentially multiple states during the DB and OL study periods. The MMRM analysed patient-visit level data, where the progression and treatment status of each patient was determined on an empirical (time-varying) basis. Placebo switch was formally incorporated in the model but dose escalation was not (i.e. utility measures were not separately assessed during ripretinib BID treatment).

b) The model statement is as follows:

EQ-5D3LUK = TRTARM STATUS PHASE TRTARM*STATUS
TRTARM*PHASE STATUS*PHASE TRTARM*STATUS*PHASE

Where:

EQ-5D3LUK = utility (Hernandez-Alava)

TRTARM = last study treatment received prior to visit (Ripretinib OD or BID/ placebo)

STATUS = subject on study treatment at visit (on / off)

PHASE = subject progressed on or prior to visit (PF / PD)

To account for intra-subject correlations, a compound symmetry covariance structure was employed. In addition, the model allowed for differences in underlying (co-)variance across the eight possible treatment-progression states. The Kenward-Roger method for calculating the denominator degrees of freedom was employed for inference. Observed marginals were used in calculation of mean utilities per health state.

The SAS code used for this analysis is approximately as follows:

```
proc mixed data = AD1;

class USUBJID TRTARM STATUS PHASE;

model EQ-5D3LUK = TRTARM STATUS PHASE TRTARM*STATUS
TRTARM*PHASE STATUS*PHASE TRTARM*STATUS*PHASE / ddfm=kr;

repeated / subject=USUBJID type=CS group=TRTARM*STATUS*PHASE;

lsmeans STATUS*PHASE /* for Total (marginalised over treatment) */
TRTARM*STATUS*PHASE /* for individual treatment group estimates */

run;
```

Table 13: MMRM Analysis of EQ-5D-3L utility values (UK mapped) - Model Estimates; ITT Population (N=129)

Model term	Treatment	Treatment status	Progression status	Estimate (SE)	DoF	p-value
Intercept				0.710 (0.036)	36.8	<0.001
TRTARM	Ripretinib 150 mg			0.036 (0.040)	55.3	0.370
STATUS		Off treatment		-0.013 (0.054)	77.5	0.812
PHASE			PD	-0.008 (0.057)	47.6	0.894
TRTARM* STATUS	Ripretinib 150 mg	Off treatment		-0.021 (0.062)	127.1	0.738
TRTARM* PHASE	Ripretinib 150 mg		PD	-0.040 (0.064)	71.1	0.533
STATUS* PHASE		Off treatment	PD	-0.010 (0.096)	55.6	0.915
TRTARM* STATUS* PHASE	Ripretinib 150 mg	Off treatment	PD	-0.061 (0.116)	99.6	0.602

Abbreviations: EQ-5D-5L = EuroQoL-Five Dimensions-Five Levels; DoF = Degrees of freedom; PD = Progressive disease; SE = Standard error
Completed EQ-5D-5L questionnaires were mapped to EQ-5D-3L UK utilities as presented in Hernandez-Alava et al. (2022).³⁵

c) The model was chosen to allow for mean utility estimation in the eight ($=2*2*2$) possible health states, hence the inclusion of all main effects as well as all two- and three-way interactions. The model also allowed for the (co-)variance of each of the 8 health states to vary.

This was essentially the most parsimonious MMRM model that would allow for full flexibility in health-state utility estimations, whilst avoiding the potential risk of over-fitting. Hence, no other baseline or time-varying covariates were adjusted for.

Given that this was the only MMRM model considered, comparison of model fit criteria (e.g. AIC) were not utilised. Model convergence was obtained.

d) Table 14 presents the number of data points (as number of visits and number of patients) that informed the final utility values in the model base case.

Table 14: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% CI	Number of visits	Number of patients
PF	0.722 (0.2171)	0.684 – 0.759	924	126
PD (BSC)	0.624 (0.2838)	0.540 – 0.708	46	43
PD on treatment	0.699 (0.2176)	0.656 – 0.741	550	79
PD off treatment	0.624 (0.2838)	0.540 – 0.708	46	43

Abbreviations: BSC = Best supportive care; CI = Confidence intervals; N/A = Not applicable; PD = Progressed disease; PF = Progression -free

Adverse events (AEs)

B15. CS, Sections 2.11.1 and 3.4.4, pages 90-91 and 133. The model only includes the incidence of Grade 3/4 treatment-emergent adverse events (TEAEs) which occurred in $\geq 5\%$ of patients in either treatment arm in the double-blind phase of INVICTUS. Please also include in the model the impact of adverse events (AEs) on costs and HRQoL from the open-label period.

Event rates for Grade 3/4 AEs occurring in $\geq 5\%$ of patients in the open-label period of INVICTUS have been calculated and included the corresponding cost and utility inputs for these events in the revised model (scenario included in Table 21). As with the AE modelling in the double-blind phase of the trial, we captured these costs in the first cycle of the analysis.

Costs

B16. PRIORITY. CS, Section 2.3.1, page 34. The text states: *“However, across the ITT population more than three-quarters (75.9%) of ripretinib exposure time was on single dose, with only the remaining 24.1% on BID.”* The EAG understands that in INVICTUS, patients could only escalate to BID dosing after

progression. Please re-calculate the proportion of post-progression ripretinib exposure time in the ripretinib arm of INVICTUS which was spent on BID dosing.

The total post-progression exposure time for patients randomised to ripretinib was 28.64 years; 60.1% was spent on BID dosing and 39.9% was spent QD dosing. As discussed in question B12, ripretinib usage in clinical practice is likely to be far lower than that captured in INVICTUS.

B17. CS, Section 3.5.1, page 138. The text states: “A scenario was explored whereby BSC costs were approximated from concomitant medications taken in the BSC arm of INVICTUS.” However, the results of the scenario analyses in CS Table 60 do not include this scenario analysis. Please provide the results of this analysis.

The scenario analysis referenced in the question, and in CS, Section 3.5.1, page 138, are presented in Table 15 below, and in Table 21.

Table 15: Scenario analysis using alternative best supportive care costs approximated from concomitant medications

	BSC cost (£)	Ripretinib cost (£)	Incremental cost (£)	BSC QALYs	Ripretinib QALYs	Incremental QALYs	ICER (£/QALY)
Base case using revised model	██████	██████	██████	████	████	████	£28,730
BSC costs based on INVICTUS BSC arm	██████	██████	██████	████	████	████	£28,889

Abbreviations: BSC = Best supportive care; ICER = Incremental cost-effectiveness ratio; QALYs = Quality-adjusted life years

B18. CS, Section 3.5.2, Table 46 and model trace worksheets, columns AD:AG in the ripretinib trace and AD:AE in the BSC trace. Please justify the assumption that patients would receive palliative interventions (palliative resection and radiotherapy) at treatment initiation (in the progression free (PF) state in the first model cycle) or/and when they progress. Why are these costs applied twice instead of once only at model entry?

Palliative intervention costs are only incurred in the proportions of patients input in cells N110:N113 on the Cost Inputs worksheet (for ripretinib) and cells N119:N122 on the Cost Inputs worksheet (for BSC). In the base case analysis, these proportions are set to 10% for palliative surgical resection and 20% for palliative radiotherapy. The same proportions are used in the first model cycle and in a proportion of the cohort that can unambiguously be assigned to be 'entering' the PD partition (i.e. in model cycles in which the PD partition is growing). Overall, given this scaling of costs, total costs are not being incurred twice but would instead effectively be incurred for a maximum of 20% of patients for palliative surgical resection or 40% of patients for palliative radiotherapy.

B19. CS, Section 3.5.1, Tables 44 and 45, page 138 to 141. The text states that the unit costs included in the table have been taken from the British National Formulary (BNF) (accessed January 2025). However, less expensive versions of these drugs are available from the current version of the BNF and/or the Commercial Medicines Unit's electronic Market Information Tool (eMIT). Please update all drug costs to use the least expensive versions of each drug from these sources.

The BNF and eMIT have been revisited and the lowest cost for each drug identified and included in the model (with the exception of ranitidine, which has been discontinued in the UK and is now substituted with omeprazole 10 mg BID). The revised data are presented in Table 16 and Table 17. The revised model incorporates these costs along with detailed references as to specific manufacturers and whether prices were obtained from eMIT (preferred) or the BNF (where a drug was not listed in eMIT).

Table 16: Pain management costs as per TA730/TA488

Drug, dose	% patients (PF)	% patients (PD)	Unit	Units per pack (N)	Cost per pack	Units per cycle	Cost per 28-day cycle (PF)	Cost per 28-day cycle (PD)
Co-codamol, 2 (30/500 mg) QDS	18.0%	22.0%	30/500 mg tablet	100	£2.74	224	£1.10	£1.35
Tramadol, 100 mg QDS	12.0%	14.0%	50 mg capsule	100	£2.20	224	£0.59	£0.69
Paracetamol, 1g QDS	33.0%	38.0%	500 mg tablet	100	£0.79	224	£0.58	£0.67
Morphine sulfate immediate release, 30 mg every 4 hours	20.0%	29.0%	10 mg tablet	56	£5.31	168	£3.19	£4.62
			20 mg tablet	56	£10.61	168	£6.37	£9.23
Dexamethasone, 4 mg OD	11%	19%	4 mg tablet	50	£35.97	28	£2.22	£3.83
						Total	£14.05	£20.39

Abbreviations: OD = Once daily; PD = Progressed disease; PF = Progression-free; QDS = Four times a day; TA = Technology appraisal

Table 17: Concomitant medications across ripretinib and BSC arms used in the base-case

Drug, dose	% patients (BSC)	% patients (ripretinib)	Unit	Units per pack (N)	Cost per pack	Units per cycle	Cost per 28-day cycle (BSC)	Cost per 28-day cycle (ripretinib)
Paracetamol, 500 mg QDS	60.5%	42.4%	500 mg tablet	100	£0.79	112	£0.54	£0.38
Oxycodone, 100 mg m/r BD	34.9%	31.8%	80 mg/mr tablet	56	£42.62	56	£14.87	£13.55
			20 mg m/r tablet	56	£9.84	56	£3.43	£3.13
Fentanyl, 50 µg patch every 72 hours	9.3%	12.9%	50 µg patch	5	£20.12	9	£3.49	£4.84
Morphine sulfate 10mg every 4 hours	18.6%	11.8%	10 mg/5 ml oral solution, 1 ml	300	£3.13	840	£1.63	£1.03
Hydromorphone, 1.3 mg every 4 hours	14.0%	7.0%	1.3 mg tablet	56	£8.82	168	£3.70	£1.85
Amoxicillin, 500 mg TDS	11.6%	3.5%	500 mg capsule	21	£1.17	21	£0.14	£0.04
Ciprofloxacin, 500 mg BD	11.6%	3.5%	500 mg tablet	10	£0.61	14	£0.10	£0.03
Loperamide hydrochloride, 6 mg daily	16.3%	8.2%	2 mg capsule	30	£0.65	15	£0.05	£0.03
Ondansetron, 8 mg every 12 hours	23.3%	34.1%	8 mg tablet	10	£0.67	10	£0.16	£0.23

Drug, dose	% patients (BSC)	% patients (ripretinib)	Unit	Units per pack (N)	Cost per pack	Units per cycle	Cost per 28-day cycle (BSC)	Cost per 28-day cycle (ripretinib)
Ibuprofen, 200 mg TDS	14.0%	20.0%	Ibuprofen tablet	84	£1.05	84	£0.15	£0.21
Sodium chloride 0.9% IV solution, 1500 ml/24hours once a month	11.6%	16.5%	0.9% IV infusion solution, 9 mg/1 ml, 500 ml	1	£16.06	3	£0.56	£0.79
Ranitidine, 300 mg daily (Substituted omeprazole 10 mg BD due to ranitidine discontinuation)	25.6%	31.8%	75 mg tablet (Substituted omeprazole 10 mg tablet)	12 (28)	£0.47	56	£0.24	£0.30
Macrogol, 2 sachets daily	34.9%	32.9%	sachet	30	£3.14	28	£1.02	£0.97
Docusate sodium, 100mg BD	11.6%	12.9%	100 mg capsule	30	£8.76	14	£0.14	£0.16
Sennoside A+b, 7.5mg OD	14.0%	12.9%	7.5 mg daily	60	£0.90	7	£0.01	£0.01
Metoclopramide, 10mg TDS	18.6%	22.4%	10 mg tablet	28	£0.43	21	£0.06	£0.07
Potassium chloride tabs, 600 mg BD	16.3%	12.9%	600 mg tablet	100	£67.28	56	£6.14	£4.86
Diazepam, 2 mg OD	30.2%	11.8%	2 mg tablet	28	£0.33	28	£0.10	£0.04

Drug, dose	% patients (BSC)	% patients (ripretinib)	Unit	Units per pack (N)	Cost per pack	Units per cycle	Cost per 28-day cycle (BSC)	Cost per 28-day cycle (ripretinib)
Levothyroxine, 50 µg OD	34.9%	29.4%	50 µg tablet	28	£0.33	28	£0.12	£0.10
Vitamin D, 800 IU OD	16.3%	12.9%	800 IU capsule	30	£1.67	28	£0.25	£0.20
						Total	£36.91	£32.82

Abbreviations: BD = Twice a day; BSC = Best supportive care; IU = International units; IV = Intravenous; m/r = Modified release; OD = Once a day; QDS = Four times a day; TDS = Three times a day

B20. CS, Section 3.5.2, Table 46 to 48, pages 143-145. The EAG has been unable to generate the costs shown in these tables using the current version of the NHS Cost Collection. Please address the following issues and update the economic model accordingly:

- ***Please clarify the version (and last accessed date) of the NHS Cost Collection used in the preparation of the CS and the model.***
- ***Please clarify which NHS Cost Collection currency codes were used for full blood count (FBC) and liver function test (LFT) in CS Tables 46 and 47.***
- ***Please clarify which NHS Cost Collection currency codes were used for palliative radiotherapy (currency codes SD01A to SD04A do not seem to exist in the latest version of the NHS Cost Collection).***
- ***Please update all unit costs shown in Tables 46 to 48 using the latest version of the NHS Cost Collection.***

In order:

- The 2023/24 NHS Cost Collection was used in preparation of the model. Prior to the original submission, the NHS Cost Collection was accessed in May 2025. The revised model now includes screenshots of the NHS National Cost Collection PowerBI tables that were used as the basis of each unit cost.
- The NHS Cost Collection currency codes used for FBC and LFT were PATH05 (Haematology) and PATH04 (Clinical Biochemistry) in the Directly Accessed Pathology Services section of the National Cost Collection PowerBI Dashboard. The costs are weighted averages across all Service Codes.
- SD01A-SD04A codes were used as proxy values for palliative radiotherapy in the previous single technology appraisal for ripretinib. The value used in the base case analysis was taken from the Palliative Medicine Service (Service Code 315) for a non-admitted, consultant-led, face-to-face attendance.

We have revisited Tables 46, 47, and 48 and made revisions and clarifications where necessary as shown in Table 18, Table 19, and Table 20.

Table 18: One-off health state resource use

Resource	Unit cost	Mean proportion of patients		Source
		PF	PD (on treatment)	
CT scan	£123.34	Ripretinib: 85% BSC: 24%	-	NICE TA488; NHS National Cost Collection 2023/24 (Diagnostic Imaging: activity-weighted average of Computerised Tomography Scan of Three Areas, with Contrast [RD26Z])
MRI scan	£171.08	Ripretinib: 12% BSC: 1%	-	NICE TA488; NHS National Cost Collection 2023/24 (Diagnostic Imaging: activity-weighted average of MRI codes RD01A, RD02A, RD03Z, RD04Z, RD05Z, RD06Z, and RD07Z)
Full blood count	£3.10	Ripretinib: 92% BSC: 56%	-	NICE TA488; NHS National Cost Collection 2023/24 (Directly Accessed Pathology Services: PATH05 Haematology; activity weighted average across all services: 100, 101, 160, 203, 303, 308, 370, 502, 800, 812, 822, and 999)
Liver function test	£1.53	Ripretinib: 92% BSC: 49%	-	NICE TA488; NHS National Cost Collection 2023/24 (Directly Accessed Pathology Services: PATH04 Clinical biochemistry; activity-weighted average across all services: 100, 101, 160, 302, 303, 370, 502, 800, 812, 822, and 999)
Palliative resection	£6,097.47	10%	10%	NICE TA488; (PD assumed to be same as PF); NHS National Cost Collection 2023/24 (Admitted Patient Care: activity-weighted average of costs for malignant GI tract disorders with a single intervention: FD11D, FD11E, FD11F covering daycase, elective, non-elective inpatient

Resource	Unit cost	Mean proportion of patients		Source
		PF	PD (on treatment)	
				short stay, non-elective inpatient long stay, and regular day or night admissions)
Palliative radiotherapy	£366.00	20%	20%	NICE TA488; NHS National Cost Collection (CL; Consultant led non-admitted face-to-face attendance, follow-up; service code 315; currency code WF01A

Abbreviations: BSC = Best supportive care; GI = Gastrointestinal tract; NICE = National Institute for Health and Care Excellence; PD = Progressed disease; PF = Progression-free; TA = technology appraisal

Table 19: Regular resource use per patient: monitoring and tests

Resource	Unit cost	PF		PD*		Source
		Mean number of weeks between tests	Frequency per 28-day cycle	Mean number of weeks between tests	Frequency per 28-day cycle	
CT scan	£123.34	Ripretinib: 12.1 BSC: 18.9	Ripretinib: 0.33 BSC: 0.21	14.5	0.28	NICE TA488; NHS National Cost Collection 2023/24 (Diagnostic Imaging: activity weighted average of Computerised Tomography Scan of Three Areas, with Contrast [RD26Z])
MRI scan	£171.08	Ripretinib: 19.9 BSC: 18.0	Ripretinib: 0.20 BSC: 0.22	8.0	0.50	NICE TA488; NHS National Cost Collection 2023/24 (Diagnostic Imaging: activity-weighted average of MRI codes RD01A, RD02A, RD03Z,

Resource	Unit cost	PF		PD*		Source
		Mean number of weeks between tests	Frequency per 28-day cycle	Mean number of weeks between tests	Frequency per 28-day cycle	
						RD04Z, RD05Z, RD06Z, and RD07Z)
Full blood count	£3.10	Ripretinib: 6.4 BSC: 10.9	Ripretinib: 0.63 BSC: 0.37	8.8	0.45	NICE TA488; NHS National Cost Collection 2023/24 (Directly Accessed Pathology Services: PATH05 Haematology; activity-weighted average across all services: 100, 101, 160, 203, 303, 308, 370, 502, 800, 812, 822, and 999)
Liver function test	£1.53	Ripretinib: 6.4 BSC: 11.2	Ripretinib: 0.63 BSC: 0.36	9.4	0.43	NICE TA488; NHS National Cost Collection 2023/24 (Directly Accessed Pathology Services: PATH04 Clinical biochemistry; activity weighted average across all services: 100, 101, 160, 302, 303, 370, 502, 800, 812, 822, and 999)
Outpatient care visit	£193.39	Ripretinib: 6.2 BSC: 7.9	Ripretinib: 0.65 BSC: 0.51	6.9	0.58	NICE TA488 (frequency for patients on BSC); NHS National Cost Collection 2023/24 (WF01A service code 370 Medical Oncology Service; activity weighted average across all non-admitted face-to-face attendance visit types)

Abbreviations: BSC = Best supportive care; CT = Computed tomography; MRI = Magnetic resonance imaging; NICE = National Institute for Health and Care Excellence; PD = Progressed disease; PF = Progression-free; TA = technology appraisal

Table 20: Cost of resolving TEAEs in the economic model

Grade 3-4 TEAE	2023/24 NHS National Cost Collection	NHS currency code description
Anaemia	£990.18	NHS National Cost Collection 2023/24 (Admitted Patient Care: activity-weighted average of costs of SA01G:SA01K, SA03G:SA03H, SA04G:SA04L and SA05G:SA05J across daycases, elective inpatients, non-elective inpatient long stays, non-elective inpatient short stays, and regular day or night admissions)
Abdominal pain	£728.41	NHS National Cost Collection 2023/24 (Admitted Patient Care: activity-weighted average of costs of FD05A and FD05B across daycases, elective inpatients, non-elective inpatient long stays, non-elective inpatient short stays, and regular day or night admissions)
Hypertension	£760.01	NHS National Cost Collection 2023/24 (Admitted Patient Care: activity-weighted average of costs of EB04Z across daycases, elective inpatients, non-elective inpatient long stays, non-elective inpatient short stays, and regular day or night admissions)

Abbreviations: NHS = National Health Service; TEAE = Treatment-emergent adverse event

Uncertainty analysis

B21. CS, Section 3.11.2, page 160 and Figure 36. The deterministic one-way sensitivity analysis (OWSA) presented in the CS identified the “PDOff” health state utility value as the parameter in the model with the greatest impact on the ICER. However, the EAG notes that in this analysis, the PDOff and PD (BSC) utility parameters are varied independently, although they are assumed to have the same value. Please explain why PDOff and PD were considered as independent parameters in the model, why they were varied/sampled separately, and the reason that varying the PDOff parameter has a large impact on the incremental cost-effectiveness ratio (ICER) whilst varying the PD (BSC) parameter has a much smaller effect.

The PD utility parameter applies to all patients in the BSC arm with disease progression, while the PDOff parameter applies to patients in the ripretinib arm who have experienced both disease progression and discontinued treatment. In the base case analysis, these were assumed to have the same value as patients are ostensibly in similar positions with regard to treatment options. Clinical advisors felt that patients no longer receiving active treatment after progression (PD off-treatment), independent of which arm they were originally randomised to and whether they received post-progression ripretinib, would be likely to have similar quality of life.²⁶ However, we would contend that the option to vary these parameters is useful as the treatment trajectory taken to reach the two states is different. In the revised model, we have included an option in the one-way sensitivity analysis (OWSA) to enable these parameters to be varied simultaneously in the OWSA worksheet.

That the variation in the PDOff utility parameter has a substantially larger impact on the ICER than the PD parameter is simply a function of the relative time spent in each state; in the submitted base case, patients accrued ■■■ QALYs in the PDOff partition in the ripretinib arm versus ■■■ QALYs in the PD partition in the BSC arm.

Model implementation

B22. CS, Section 3.3.2, page 121 and executable model, worksheet “Data Store”, cells D120:E220. The CS states that the general population mortality estimates

have been updated to use life tables for the UK. These life table risks appear to be contained in the worksheet “Data Store.” However, the life tables applied in the live model calculations are contained in worksheet “ERG_WeightedGenPopModel.” Please amend the model to use life tables for England only and ensure that they are linked to the live model calculations.

General population mortality estimates have been revised to include life tables specific to England and specifically using the said life table data as stored in the Data Store worksheet in cells D120:E220.

B23. PRIORITY. CS, Section 3.4.4., page 134, Executable model, worksheet “Trace (Ripretinib)”, column BU and worksheet “Trace (BSC)”, column BU. The CS states that “All AEs were assumed to occur in the first cycle of the model.” However, the QALY calculations in column BU are subject to several problems:

- (i) The disutility values are applied in every model cycle (rather than the first cycle only);*
- (ii) The use of brackets means that the AE disutility is not scaled up by the population size (amending the cohort size from 1000 to 1 in worksheet “Settings” leads to very different mean QALYs in each treatment group);*
- (iii) The AE disutility is applied only to people in the PF state after half-cycle correction (rather than all patients who start treatment with ripretinib or BSC);*
- (iv) The AE disutility is divided by 13, instead of (“cycles/time”), meaning that any changes to the cycle length are not automatically applied.*

Please confirm that these are errors and correct the model. The formulae have been amended in light of all feedback. The original assumptions reflected by these formulae, particularly the assumption of ongoing utility decrements after occurrence of the initial AE, were conservative from the ripretinib perspective given the higher incidence of hypertension and abdominal pain seen versus the BSC arm.

B24. PRIORITY. Executable model, worksheet “Clinical Inputs”, columns C, G:L and M:O. The EAG understands that the calculations contained in column L are intended to reflect the adjusted cumulative probability of OS based on the log-logistic OS model fitted to data from INVICTUS including a constraint to ensure

that the per-cycle risk of death must be as least as high as that for the age- and sex-matched general population. This constrained OS model feeds directly into the partitioned survival model trace. However, the life table constraint in column L has been implemented incorrectly. This can be seen by calculating the per-cycle risks of death from column L and comparing these risks against the general population risks in column C – the per-cycle adjusted modelled risk (from column L) is lower than the life table risk after cycle 285. An accompanying spreadsheet has been provided by the EAG to illustrate the issue. Please confirm that this is an error and correct the model.

The age- and sex-matched general population constraint was indeed not applied in the HR-adjusted OS column (column L in the “Clinical Inputs” worksheet in the submitted model). This has been addressed in the revised version of the model, which introduces an “HR adjusted mort. constrained to general population mort.” column (column L in the “Clinical Inputs” worksheet in the revised model). This column is then used as the basis of the constraint in column M in the “Clinical Inputs” worksheet in the revised model and in turn drives the calculations in the Trace worksheets.

B25. PRIORITY. Executable model, worksheet “Trace (Ripretinib)”, column V. The calculations in column V apply the cost of a new pack of 30 ripretinib tablets in every 9 model cycles, with no additional pack required in every 10th model cycle (due to the accumulated tablets in each 28-day cycle). These calculations: (a) are applied to the half-cycle corrected model trace and (b) do not account for any wastage in the base case analysis. Please amend the model to calculate acquisition costs from the uncorrected model trace and include an assumption that each patient initiating treatment with ripretinib will waste on average 0.25 packs, as was accepted by the Appraisal Committee in Technology Appraisal (TA) 881.

Relative to a simple per tablet-based approach, the adoption of an integer pack-based cost calculation approach for ripretinib resulted in analyses that show an additional cost of approximately 0.47 packs of ripretinib versus the previous approach of modelling tablet-based costs; this reflects tablet wastage with tablets remaining at the end of a pack. However, when the pack-based calculation approach is active, the model does not explicitly report wastage on the Results worksheet, but wastage is

captured implicitly. We have, however, reverted the revised model to use a flat wastage rate of 0.25 packs of ripretinib. The impact of these scenarios on the ICER are presented in Table 21.

B26. CS, Section 3.5.1, page 137 and executable model, worksheet “Trace (Ripretinib)”, columns Q, V, X and Y. The model includes a relative dose intensity (RDI) estimate of 96.5%, based on the double-blind period of INVICTUS. Please clarify why RDI estimates for post-progression ripretinib use from INVICTUS were not included in the model, given that the company is now also seeking a positive recommendation which includes the use of ripretinib post-progression (i.e., the original stopping rule proposed in TA881 has been removed).

In routine practice, post-progression use may include patients receiving both the QD and BID doses of ripretinib, which complicates derivation of an RDI across the two populations. Exclusion of the RDI from the ripretinib pack-based price calculation was a conservative assumption from the ripretinib perspective. An option has now been incorporated into the model to also capture RDI in the post-progression period.

B27. Executable model, worksheets “Trace (Ripretinib)” and “Trace (BSC)”, columns V to Z. Regarding the costs of pre-treatment for patients receiving ripretinib and BSC, please confirm that these are errors and correct the model, as necessary:

- The pre-treatment cost applied to the PF state is not scaled up by the population size (the cost is included outside of the brackets in the formula which multiplies the drug treatment costs by the probabilities/numbers from the trace).*
- The pre-treatment cost is also applied to the PD states (PD_{on} and PD_{off} for patients receiving ripretinib and PD for patients receiving BSC) in the first cycle of the model, based on the half-cycle corrected model trace. This contradicts the information in CS, Section 3.5.2, Table 46, whereby the text suggests that the pre-treatment costs are applied as a lump-sum cost in the first model cycle to all patients starting ripretinib or BSC in the PFS state in the first model cycle.*

Pre-treatment costs in the PF state are now multiplied by the patient number specified on the Settings worksheet. The pre-treatment costs cover CT scans, MRI scans, full blood count, and liver function tests. Some, but not all of these, may be performed either at the time of treatment initiation or dose escalation and could therefore be explored in sensitivity or scenario analysis. However, the model has been aligned with the caption for Table 46 in the CS and pre-treatment costs are captured only in the first cycle of the model, in the PF partition, and based on the model trace prior to half-cycle correction.

B28. Executable model, worksheet “Trace (Ripretinib)”, columns V, X and Y. The formulae in column V include BSC costs for patients who are progression-free, but the formulae in columns X and Y exclude BSC costs for patients who have progressed. Please confirm that these are errors and correct the model.

In the submitted model, BSC costs in the ripretinib arm were captured at two ‘intensities’ covering progression-free patients and patients with progressed disease. Progressed disease BSC costs were only captured for progressed disease off-treatment patients in the base case analysis as data were not available on BSC treatment costs associated with the post-progression on-treatment state. However, formulae in columns X and Y have been amended to capture the same post-progression BSC costs as the post-progression off-treatment partition state (column Z in the “Trace (Ripretinib)” worksheet).

B29. Worksheet “Trace (Ripretinib)” columns AD:AG and worksheet “Trace (BSC)”, columns AD:AE. The palliative care (palliative resection and palliative radiotherapy) cost for the PF state is based on the half-cycle corrected model trace, but the cost in the PD state is based on the uncorrected trace. This applies to both the ripretinib and BSC traces. Please confirm that these are errors and correct the model.

The initial rationale for palliative care costs in the PD state being based on the uncorrected trace was driven by the notion that such costs would be incurred immediately at the start of each model cycle as patients ‘transition’ into the PD partitions. However, we accept that the PF and PD states should be aligned in this regard to avoid a half-cycle of double counting of palliative care costs. The model has,

therefore, been amended to base all palliative care costs on the half-cycle corrected model traces.

B30. Worksheet “Trace (Ripretinib)”, column AB. The formula which calculates the total treatment costs for ripretinib does not include the values in column Y (costs of treatment in PDOn (BID Dosing)), which leads to the total treatment costs to decrease if the proportion of PD on-treatment patients requiring BID dosing is included in ‘Cost inputs’ cell F24. Please confirm that this is an error and correct the model.

The formulae in column AB of the “Trace (Ripretinib)” worksheet do not drive the calculation of the overall cost of ripretinib or the calculation of the ICER, and are only used for the purpose of calculating a subtotal that is not used in any downstream calculations. However, this did previously only reflect the costs of ripretinib QD and so the formulae in column AB have been updated accordingly.

B31. PRIORITY. Executable model, worksheet “Model Parameters”, cells D51:54. The probabilistic sampling routine does not account for logical ordering of the health states and the sampled utility value for the PD off treatment states can be higher than that for the sampled utility value for the PF states. Ren *et al.* (*Pharmacoeconomics*, 2018, vol. 36[3]) have proposed a method for sampling ordered parameters, including utility values. Please apply this method in the model using the variance-covariance matrix from the MMRM.

We have implemented the Ren *et al.* methodology for ensuring the logical ordering of the PD state utilities relative to the PF state utility.³⁶ We have followed the approach outlined in the Ren *et al.* manuscript and supplementary materials, which utilises the logit transformed central estimates of the utility value (and the variance around the central estimate) to inform the difference distribution.³⁶ We have assumed, as in Ren *et al.*, that the difference distribution follows a gamma distribution, while the reference distribution follows a beta distribution, with the latter in line with the submitted base case.³⁶

B32. Executable model, worksheet “Cost Inputs”, cell F127 and H129. The end-of-life care cost in cell H129 does not update when alternative cost sources are selected from the drop-down menu in cell F127. Please correct this error.

The formulae in the model have been updated such that the drop-down menu for end-of-life care updates the value in cell H129 (scenario provided in Table 21).

B33. Executable model, worksheets “Trace (Ripretinib)” and “Trace (BSC)”, column C. Each cycle is assumed to be 1/13 years in duration. The calculations in this column assume that there are 52 weeks in a year. However, there are approximately 52.17 weeks in a year. Please correct the model, if possible.

It is acknowledged that the 28-day cycle length results in a ~0.34% (1.25 day) mismatch between model year length and calendar year length (assuming an average of 365.25 days per year). However, given the time constraints and structural changes that would be required to address this, no changes have been made to the model to address this discrepancy.

Summary table of selected scenario analyses after model revisions

Table 21: Summary of scenario analyses after model revisions

	BSC cost (£)	Ripretinib cost (£)	Incremental cost (£)	BSC QALYs	Ripretinib QALYs	Incremental QALYs	ICER (£/ QALY)
Base case using revised model	██████	██████	██████	████	████	████	£28,730
B12 Including 50% BID use in the PDOn state	██████	██████	██████	████	████	████	£32,645
B15 Without open-label period AEs	██████	██████	██████	████	████	████	£28,747
B17 BSC costs based on INVICTUS BSC arm	██████	██████	██████	████	████	████	£28,889
B25 Pack-based cost calculations off (on in the revised base case)	██████	██████	██████	████	████	████	£29,672
B32 Alternative end-of-life care costs (Round <i>et al.</i>)	██████	██████	██████	████	████	████	£28,830

Abbreviations: BSC = Best supportive care; ICER = Incremental cost-effectiveness ratio; QALYs = Quality-adjusted life years

Revised model includes all structural revisions as requested in questions B21 to B33, the option to capture open-label period adverse events as requested in question B15, and revised cost inputs as requested in question B19

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments (review of TA881) [ID6496]

Clarification questions

June 2025

File name	Version	Contains confidential information	Date
ID6496 Ripretinib clarification letter response_noCON_B9	V.1	No	7th July 2025

Section A: Clarification on effectiveness data

SLR for clinical evidence

A1. Company's submission (CS) Appendix B, Section 2, pages 34-50. With reference to the systematic literature review (SLR) of clinical effectiveness evidence, please provide details of the number of reviewers involved and the methods used for screening citations and full-text articles, extracting data, and assessing study quality.

[Answer provided in responses delivered on 30th June 2025]

Clinical effectiveness evidence

A2. CS, Section 2.6.2, pages 54 to 55 and Figure 4. The text states that at the 10th August 2020 data cut-off (DCO), 65 patients in the ripretinib group had progressed, of whom 43 dose escalated to ripretinib 150mg twice daily (BID) and 22 patients either continued ripretinib 150mg Once daily (QD) or discontinued study treatment. Please clarify how many of the 22 patients continued ripretinib 150mg QD and how many discontinued.

[Answer provided in responses delivered on 30th June 2025]

A3. PRIORITY. CS, Section 2.6.2, page 54. The text states "*As of January 2021, 63 of the 85 patients originally randomised to ripretinib had entered the open label period following disease progression based on independent radiological review. Of those, 19 continued to receive 150 mg QD and 44 underwent Inter-patient Dose Escalation (IPDE) to 150 mg BID.*" Please provide information on the duration of post-progression ripretinib treatment at each dose (mean, standard deviation and range).

[Answer provided in responses delivered on 30th June 2025]

A4. CS, Section 2.62, page 75. The CS states that health-related quality of life (HRQoL) in INVICTUS was assessed using the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ C30) role and physical functioning domains, the Euroqol 5-Dimensions 5-Level (EQ-5D-5L) and the Euroqol Visual Analogue Scale (EQ VAS) from

baseline to only Cycle 2 Day 1 and that this was due to the small number of patients after this time point. Please clarify why only a small number of patients were evaluated for HRQoL at later cycles.

[Answer provided in responses delivered on 30th June 2025]

A5. CS, Section 2.3.2, Table 8, page 38. Please provide a breakdown of the number of patients with an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 1 and the number of patients with an ECOG PS of 2 in INVICTUS.

[Answer provided in responses delivered on 30th June 2025]

A6. PRIORITY. CS, Section 2.3.3, Table 8, page 38. Despite randomisation being stratified by ECOG PS in INVICTUS, the placebo group had slightly worse PS scores and older age. Please comment on the potential implications of this imbalance.

[Answer provided in responses delivered on 30th June 2025]

A7. CS, Section 2.8.1, Figure 21, page 88. The subgroup analysis of progression-free survival (PFS) in INVICTUS suggests that patients with ECOG PS 0 had a worse treatment effect of ripretinib compared to those with ECOG PS 1–2. Also, older patients appear to have a greater treatment effect. These results appear counterintuitive, please comment on these findings.

[Answer provided in responses delivered on 30th June 2025]

A8. CS, Section 2.3.4, pages 39-44. Please undertake a quality assessment of the Royal Marsden Expanded Access Cohort study using an appropriate tool given the study design.

[Answer provided in responses delivered on 30th June 2025]

A9. PRIORITY. CS, Section 2.3.4, Table 11, page 43 and Section 2.6.3, pages 82 to 86. Table 11 summarises the characteristics of the full real-world evidence (RWE) cohort, where 42% of the cohort received only two prior lines of treatment before ripretinib. If possible, please update Table 11 and Section 2.6.3 to reflect the subgroup with three prior lines of treatment, for a more appropriate comparison with the population relevant to this submission.

[Answer provided in responses delivered on 30th June 2025]

Section B: Clarification on cost-effectiveness data

Survival analysis

B1. PRIORITY. CS, Section 3.3, pages 108-128. The data for TTD, PFS and OS used in the economic model reflect the January 2021 DCO of INVICTUS. Please clarify whether more recent data-cuts are available, and if so, why these have not been used.

[Answer provided in responses delivered on 30th June 2025]

B2. PRIORITY. CS, Section 3.3.3, page 127. Time to treatment discontinuation (TTD) is modelled as a composite endpoint including treatment discontinuation on either QD or BID dosing and disease progression as events.

(a) Please include further details about how the composite endpoint of PFS+TTD was calculated, including details of what was counted as an event and how censoring rules were applied.

(b) Please clarify why it was necessary to include PFS in the composite endpoint – why was time to treatment discontinuation not instead analysed as the time from study entry through to discontinuation on the last received dose of ripretinib in either the double-blind or open-label periods of INVICTUS?

(c) Section 2.4.1 on page 47 of the CS describes a post hoc TTD analysis, including any dose discontinuation during both the double-blind and open-label periods. The TTD definitions and calculations appear inconsistent between Sections 2.4.1 and 3.3.3. Why was the analysis in Section 2.4.1 not used as the base case? If these are separate analyses, please clarify the differences and explain which estimates were used in the model.

[Answer provided in responses delivered on 30th June 2025]

B3. PRIORITY. CS, Section 2.6.2, Figure 10, page 65. For non-escalating patients in INVICTUS, the EAG understands that they either remained on ripretinib 150mg QD post-progression or received no further treatment and that the survival of these patients is calculated from the start of the trial. For those who escalated

to ripretinib 150mg BID, survival appears to be measured from the first BID dose post-progression. Such comparisons are based on survival from different baselines (time of study entry and time of progression, respectively). This likely leads to immortal time bias, which cannot be corrected through statistical methods alone. Please clarify the following:

- (a) Is this analysis limited to patients randomised to the ripretinib treatment arm?*
- (b) Given the risk of immortal time bias, how should this analysis be interpreted?*
- (c) Please perform an updated analysis of post-progression survival from the first QD vs. BID dose among patients in the ripretinib arm after progression (assuming similar time from progression to next treatment in both cases), and report patient characteristics at the secondary baseline for the naïve comparison (at a minimum, report the covariates at secondary baseline used in the two-stage IPDE adjustment, including: time to progression, ECOG performance status at progression, EQ-5D VAS score at progression, and age at baseline), if feasible.*

[Answer provided in responses delivered on 30th June 2025]

B4. PRIORITY. CS, Section 2.6.2, pages 63 to 72. Please clarify whether all *post hoc* OS analyses aimed at quantifying the IPDE effect were designed to weight or adjust patients who received ripretinib 150mg BID post-progression (44 patients as of January 2021) as if they had received 150mg QD. If not, please clarify the estimand for each analysis.

[Answer provided in responses delivered on 30th June 2025]

B5. PRIORITY. CS, Section 2.6.2, pages 63 to 72. Given that 97% of patients (63/65) who progressed received continued ripretinib (i.e., much higher than the 80% suggested by the clinicians consulted by the company), please also clarify whether post-progression QD ripretinib would alter the shape of the survival curve compared to those who received no further treatment.

[Answer provided in responses delivered on 30th June 2025]

B6. PRIORITY. CS, Section 2.6.2, Figure 12, page 68. Is the analysis illustrated in Figure 12 related to the analysis described on page 122 of the CS (“Censored BID-dosing analysis”)? If not, please clarify how the analyses differ from one another and explain which analysis is included in the scenario analyses in CS Table 60.

[Answer provided in responses delivered on 30th June 2025]

B7. PRIORITY. CS, Section 2.6.2, page 68. Please clarify whether the Cox proportional hazards time-varying analysis for ripretinib 150mg QD includes only the QD period after progression. If not, please explain what data were included in the analysis (including any reprocessing of those data).

[Answer provided in responses delivered on 30th June 2025]

B8. PRIORITY. CS, Appendix J, Figure 11, page 109. Please update the hazard plot for the composite endpoint of PFS+TTD to include the empirical smoothed hazard.

[Answer provided in responses delivered on 30th June 2025]

B9. PRIORITY. CS, Section 3.3.2, Table 36, page 124. With respect to the two-stage adjustment to account for the IPDE effect on OS in Table 36, please provide results from the Gompertz model for simple and complex adjustment models, and provide the following for all models:

- (a) Overlays of the different parametric survival models with the Kaplan-Meier estimates, for both the simple and complex adjustment models.*
- (b) Empirical hazard ratios of these models.*
- (c) Plots showing the empirical unsmoothed hazard, empirical smoothed hazard and modelled hazards.*

(d) An explanation of the interpretation of survival time ratio estimates presented in this table.

(e) Please explain why the company did not instead first adjust the OS data and then fit parametric models to those adjusted data (as was done for the placebo group switching adjustment). Please conduct this analysis in a way which is consistent with the placebo group switching adjustment using the 2-stage estimation method.

Table 1 is an update of Table 36 including the Gompertz model.

Table 1: Post-progression survival time ratio estimates and AIC goodness-of-fit measures for a two-stage adjustment to estimate the effect of IPDE

Covariate adjustment approach	Distribution	AIC	Survival time ratio estimate (95% CI)
Simple	Exponential	166.53	2.44 (1.19, 5.01)
	Weibull	167.78	2.68 (1.16, 6.15)
	Log-normal	159.96	3.45 (1.56, 7.60)
	Log-logistic	160.26	4.28 (1.90, 9.64)
	Generalised gamma	160.90	3.21 (1.48, 6.97)
	Gompertz	168.54	2.44 (1.19, 5.01)
Complex	Exponential	158.70	1.95 (0.72, 5.25)
	Weibull	160.70	1.94 (0.71, 5.34)
	Log-normal	149.51	2.40 (1.10, 5.25)
	Log-logistic	150.50	2.34 (1.03, 5.29)
	Generalised gamma	144.51	2.72 (1.57, 4.74)
	Gompertz	156.98	1.96 (0.73, 5.27)

Notes: Survival time ratios >1 indicate longer post-progression survival with ripretinib BID versus QD.
Abbreviations: AIC - Akaike information criterion; CI - Confidence interval; IPDE - Inpatient dose escalation;
OS – Overall survival.

a) For each of the Stage 1 models in Table 1 above, counterfactual ripretinib 150mg QD survival times were calculated with and without re-censoring. Counterfactual OS times (from randomisation) were calculated for IPDE subjects with the aim of estimating how long they would have survived had they not dose escalated to BID. These counterfactual OS times from the IPDE patients were then combined with

the observed OS times from the non-IPDE patients and subsequently analysed. Note that patients randomised to placebo were excluded from these analyses. The following parametric survival models were fitted to each set of (counterfactual) OS times: exponential, gamma, generalised gamma, Gompertz, log-logistic, log-normal, and Weibull. Kaplan-Meier plots of the counterfactual and the unadjusted (observed) survival times are presented, overlaid with the fitted parametric survival models, separately for each set of counterfactual OS times. These are presented in the reference pack of this response (file name “os_itt_all_aft_km_haz_dcc_all_f”).¹

- b) Hazard ratios of the unadjusted (observed) OS times compared with the counterfactual OS times (restricted to patients randomised to ripretinib 150mg QD who subsequently switched to BID) are presented in Table 2.

Table 2: Cox proportional hazards regression of time to overall survival from randomisation (counterfactuals from two-stage estimation models), Full Analysis Set subjects randomised to ripretinib 150mg QD who later dose escalated to receive ripretinib 150mg BID (N=44)

With or without re-censoring	Covariate adjustment approach	Parametric model	Observed vs Counterfactual HR (95% CI)
With re-censoring	Simple	Exponential	0.51 (0.35, 0.73)
		Weibull	0.45 (0.29, 0.69)
		Log-normal	0.36 (0.20, 0.67)
		Log-logistic	0.44 (0.27, 0.71)
		Generalised gamma	0.38 (0.22, 0.67)
		Gompertz	0.51 (0.35, 0.73)
	Complex	Exponential	0.69 (0.55, 0.86)
		Weibull	0.69 (0.55, 0.86)
		Log-normal	0.52 (0.36, 0.74)
		Log-logistic	0.54 (0.39, 0.75)
		Generalised gamma	0.44 (0.28, 0.68)
		Gompertz	0.68 (0.54, 0.85)
Without re-censoring	Simple	Exponential	0.65 (0.54, 0.79)
		Weibull	0.62 (0.51, 0.77)

		Log-normal	0.59 (0.46, 0.74)
		Log-logistic	0.56 (0.44, 0.71)
		Generalised gamma	0.60 (0.48, 0.75)
		Gompertz	0.65 (0.54, 0.79)
	Complex	Exponential	0.72 (0.62, 0.84)
		Weibull	0.72 (0.62, 0.84)
		Log-normal	0.65 (0.54, 0.79)
		Log-logistic	0.66 (0.55, 0.80)
		Generalised gamma	0.62 (0.50, 0.76)
		Gompertz	0.72 (0.61, 0.84)

Notes:

Cox PH model adjusting for event time source (observed vs CF from two-stage estimation models).

CF survival times represent 'pure' ripretinib QD, i.e. following the removal of any ripretinib BID effect.

Hazard ratio less (greater) than one indicates a reduction (increase) in the risk of death following a switch to ripretinib BID.

Variance of log (Hazard ratio) from a robust sandwich estimator to account for within-subject paired survival times.

Abbreviations: BID - Twice-daily; CF - Counter-factual; CI - Confidence interval; HR – Hazard ratio; QD - Once-daily.

- c) For each set of (counterfactual) ripretinib 150mg QD survival times, the empirical unsmoothed hazard, a smoothed hazard, and the modelled hazards are plotted. These are presented in the reference pack of this response (file name "CONFIDENTIAL_os_itt_all_aft_km_fit_dcc2_all_f").²
- d) The time ratios in CS Table 36 and Table 1 can be considered as a comparison of BID vs QD post-progression survival in patients randomised to ripretinib 150mg QD who progressed. The time ratios range between approximately 2 to 4. A time ratio of 2 can be interpreted as an increase in survival time post progression due to BID (vs QD) by a factor of 2. The time ratio is the inverse of the acceleration factor (see part e) response below.
- e) It should be noted that switching from QD to BID is an inherently different challenge compared with the switch from placebo to QD. Estimation of the potential impact of IPDE involves consideration of the transition from one treatment (QD) to two (i.e. remaining on QD or dose escalating to BID). Estimation of the potential impact of placebo switch involves consideration of the transition from placebo to one of two treatments (placebo, QD). An important statistical consideration is that in the latter scenario we are trying to estimate the effect of the first treatment (i.e. placebo), whereas in the former the aim is to estimate the effect of the second treatment (i.e.

BID). As such, many typical treatment switching adjustment methods, especially those that rely on randomisation, are not appropriate (e.g. RPSFTM) or readily interpretable for this latter IPDE scenario. For example, we cannot reliably estimate the effect of BID on overall survival under the assumption that patients were randomised to BID at study start. However, the 2-stage estimation method has been applied to the ripretinib 150mg QD arm to determine counterfactual ripretinib 150mg QD survival times in a similar manner to the placebo switching 2-stage adjustment. All of these parametric models are now incorporated into the model and can be run using the “Scenario analyses” and “BID OS analyses” menus on the Settings worksheet. The “Two-stage adjusted BID models” option must be selected from the “Scenario analyses” menu, and the individual two-stage adjustment models can then be selected from the “Two-stage adjusted BID models” menu.

In the first stage, accelerated failure time models (exponential, Weibull, log-normal, log-logistic, generalised Gamma and Gompertz, including simple and complex covariate adjustment measured at the time of progression and including a covariate indicating treatment switch to BID) were fitted to the post-progression survival time in patients randomised to ripretinib 150mg QD in order to estimate the treatment effect in patients who switched compared to those who did not. The resulting acceleration factors were then used to shrink the post-progression survival times in patients who switched in order to estimate counterfactual OS times (i.e. unaffected by switching to BID).

Stage 1 model fit was assessed via AICs and clinical plausibility (the complex generalised gamma had convergence problems so was not considered). The model considered to have the best fit was the simple, log-normal, with re-censoring and was subsequently used in the updated cost-effectiveness model as a sensitivity case. Parametric models have now been fitted to each set of counterfactual OS times as described in part a) above.

B10. PRIORITY. CS, Section 3.3.2, Table 34, page 122. Within the censored BID-dosing analysis, OS is assessed in two sub-populations based on post-progression treatment (IPDE vs. QD). Since this comparison is non-randomised

and the groups differ in size, there is a risk of selection bias. Please comment on the potential impact of this selection bias on the interpretation of OS results.

[Answer provided in responses delivered on 30th June 2025]

B11. PRIORITY. CS, Section 3.3.2, page 121. The CS states “Beyond the goodness of fit statistics, the loglogistic model extrapolation predicts that 8.6% of patients in the ripretinib arm would be alive at 10 years, which is in line with the upper end of estimates stated at a clinical advisory board held in July 2024.” However, the minutes of the 2024 advisory board meeting state [REDACTED]

[REDACTED] Please provide further justification for the selection of the log-logistic OS model.

[Answer provided in responses delivered on 30th June 2025]

B12. PRIORITY. CS, Section 3.7, page 149. The base case model uses the unadjusted OS data from INVICTUS and assumes that the outcomes observed in the trial can be achieved using QD dosing (i.e., without escalation to BID dosing). This introduces an inconsistency between the what happened in the trial and the costs applied in the model. Please explain why the model scenario “Cost of ripretinib BID captured in 50% of patients remaining on treatment after progression” in CS Table 16 was not applied in the base case?

[Answer provided in responses delivered on 30th June 2025]

B13. PRIORITY. CS, Section 3.3.3, Figure 32, page 127. Please provide the summary Kaplan-Meier estimates (in the same format as those provided in the executable model, worksheet “KM Data”) for the composite outcome of PFS+TTD which is used in the economic model.

[Answer provided in responses delivered on 30th June 2025]

Health-related quality of life (HRQoL)

B14. PRIORITY. CS, Section 3.4.5, pages 134 to 136. With respect to the mixed model for repeated measures (MMRM) analysis of the utility data in INVICTUS:

- ***Please clarify how switching in the control arm and dose escalation in the treatment arm were handled in the analysis of utilities for progressed disease (PD) for, BSC, PD on treatment, and PD off treatment?***
- ***Please also provide the full model specification of the MMRM (ideally as a formula) and report the relevant coefficients.***
- ***Please justify the preferred MMRM regression model specification, particularly the selection of regression covariates and how the model fit was assessed.***
- ***Please clarify the number of data points available for progression-free (PF), PD (BSC), PD on treatment and PD off treatment to inform the MMRM analysis.***

[Answer provided in responses delivered on 30th June 2025]

Adverse events (AEs)

B15. CS, Sections 2.11.1 and 3.4.4, pages 90-91 and 133. The model only includes the incidence of Grade 3/4 treatment-emergent adverse events (TEAEs) which occurred in $\geq 5\%$ of patients in either treatment arm in the double-blind phase of INVICTUS. Please also include in the model the impact of adverse events (AEs) on costs and HRQoL from the open-label period.

[Answer provided in responses delivered on 30th June 2025]

Costs

B16. PRIORITY. CS, Section 2.3.1, page 34. The text states: “However, across the ITT population more than three-quarters (75.9%) of ripretinib exposure time was on single dose, with only the remaining 24.1% on BID.” The EAG understands that in INVICTUS, patients could only escalate to BID dosing after

progression. Please re-calculate the proportion of post-progression ripretinib exposure time in the ripretinib arm of INVICTUS which was spent on BID dosing.

[Answer provided in responses delivered on 30th June 2025]

B17. CS, Section 3.5.1, page 138. The text states: “A scenario was explored whereby BSC costs were approximated from concomitant medications taken in the BSC arm of INVICTUS.” However, the results of the scenario analyses in CS Table 60 do not include this scenario analysis. Please provide the results of this analysis.

[Answer provided in responses delivered on 30th June 2025]

B18. CS, Section 3.5.2, Table 46 and model trace worksheets, columns AD:AG in the ripretinib trace and AD:AE in the BSC trace. Please justify the assumption that patients would receive palliative interventions (palliative resection and radiotherapy) at treatment initiation (in the progression free (PF) state in the first model cycle) or/and when they progress. Why are these costs applied twice instead of once only at model entry?

[Answer provided in responses delivered on 30th June 2025]

B19. CS, Section 3.5.1, Tables 44 and 45, page 138 to 141. The text states that the unit costs included in the table have been taken from the British National Formulary (BNF) (accessed January 2025). However, less expensive versions of these drugs are available from the current version of the BNF and/or the Commercial Medicines Unit’s electronic Market Information Tool (eMIT). Please update all drug costs to use the least expensive versions of each drug from these sources.

[Answer provided in responses delivered on 30th June 2025]

B20. CS, Section 3.5.2, Table 46 to 48, pages 143-145. The EAG has been unable to generate the costs shown in these tables using the current version of the NHS Cost Collection. Please address the following issues and update the economic model accordingly:

- ***Please clarify the version (and last accessed date) of the NHS Cost Collection used in the preparation of the CS and the model.***

- ***Please clarify which NHS Cost Collection currency codes were used for full blood count (FBC) and liver function test (LFT) in CS Tables 46 and 47.***
- ***Please clarify which NHS Cost Collection currency codes were used for palliative radiotherapy (currency codes SD01A to SD04A do not seem to exist in the latest version of the NHS Cost Collection).***
- ***Please update all unit costs shown in Tables 46 to 48 using the latest version of the NHS Cost Collection.***

[Answer provided in responses delivered on 30th June 2025]

Uncertainty analysis

B21. CS, Section 3.11.2, page 160 and Figure 36. The deterministic one-way sensitivity analysis (OWSA) presented in the CS identified the “PDOff” health state utility value as the parameter in the model with the greatest impact on the ICER. However, the EAG notes that in this analysis, the PDOff and PD (BSC) utility parameters are varied independently, although they are assumed to have the same value. Please explain why PDOff and PD were considered as independent parameters in the model, why they were varied/sampled separately, and the reason that varying the PDOff parameter has a large impact on the incremental cost-effectiveness ratio (ICER) whilst varying the PD (BSC) parameter has a much smaller effect.

[Answer provided in responses delivered on 30th June 2025]

Model implementation

B22. CS, Section 3.3.2, page 121 and executable model, worksheet “Data Store”, cells D120:E220. The CS states that the general population mortality estimates have been updated to use life tables for the UK. These life table risks appear to be contained in the worksheet “Data Store.” However, the life tables applied in the live model calculations are contained in worksheet “ERG_WeightedGenPopModel.” Please amend the model to use life tables for England only and ensure that they are linked to the live model calculations.

[Answer provided in responses delivered on 30th June 2025]

B23. PRIORITY. CS, Section 3.4.4., page 134, Executable model, worksheet “Trace (Ripretinib)”, column BU and worksheet “Trace (BSC)”, column BU. The CS states that *“All AEs were assumed to occur in the first cycle of the model.”* However, the QALY calculations in column BU are subject to several problems:

- (i) The disutility values are applied in every model cycle (rather than the first cycle only);*
- (ii) The use of brackets means that the AE disutility is not scaled up by the population size (amending the cohort size from 1000 to 1 in worksheet “Settings” leads to very different mean QALYs in each treatment group);*
- (iii) The AE disutility is applied only to people in the PF state after half-cycle correction (rather than all patients who start treatment with ripretinib or BSC);*
- (iv) The AE disutility is divided by 13, instead of (“cycles/time”), meaning that any changes to the cycle length are not automatically applied.*

Please confirm that these are errors and correct the model.

[Answer provided in responses delivered on 30th June 2025]

B24. PRIORITY. Executable model, worksheet “Clinical Inputs”, columns C, G:L and M:O. The EAG understands that the calculations contained in column L are intended to reflect the adjusted cumulative probability of OS based on the log-logistic OS model fitted to data from INVICTUS including a constraint to ensure that the per-cycle risk of death must be as least as high as that for the age- and sex-matched general population. This constrained OS model feeds directly into the partitioned survival model trace. However, the life table constraint in column L has been implemented incorrectly. This can be seen by calculating the per-cycle risks of death from column L and comparing these risks against the general population risks in column C – the per-cycle adjusted modelled risk (from column L) is lower than the life table risk after cycle 285. An accompanying spreadsheet has been provided by the EAG to illustrate the issue. Please confirm that this is an error and correct the model.

[Answer provided in responses delivered on 30th June 2025]

B25. PRIORITY. Executable model, worksheet “Trace (Ripretinib)”, column V. The calculations in column V apply the cost of a new pack of 30 ripretinib tablets in every 9 model cycles, with no additional pack required in every 10th model cycle (due to the accumulated tablets in each 28-day cycle). These calculations: (a) are applied to the half-cycle corrected model trace and (b) do not account for any wastage in the base case analysis. Please amend the model to calculate acquisition costs from the uncorrected model trace and include an assumption that each patient initiating treatment with ripretinib will waste on average 0.25 packs, as was accepted by the Appraisal Committee in Technology Appraisal (TA) 881.

[Answer provided in responses delivered on 30th June 2025]

B26. CS, Section 3.5.1, page 137 and executable model, worksheet “Trace (Ripretinib)”, columns Q, V, X and Y. The model includes a relative dose intensity (RDI) estimate of 96.5%, based on the double-blind period of INVICTUS. Please clarify why RDI estimates for post-progression ripretinib use from INVICTUS were not included in the model, given that the company is now also seeking a positive recommendation which includes the use of ripretinib post-progression (i.e., the original stopping rule proposed in TA881 has been removed).

[Answer provided in responses delivered on 30th June 2025]

B27. Executable model, worksheets “Trace (Ripretinib)” and “Trace (BSC)”, columns V to Z. Regarding the costs of pre-treatment for patients receiving ripretinib and BSC, please confirm that these are errors and correct the model, as necessary:

- *The pre-treatment cost applied to the PF state is not scaled up by the population size (the cost is included outside of the brackets in the formula which multiplies the drug treatment costs by the probabilities/numbers from the trace).*
- *The pre-treatment cost is also applied to the PD states (PD_{on} and PD_{off} for patients receiving ripretinib and PD for patients receiving BSC) in the first cycle of the model, based on the half-cycle corrected model trace. This contradicts the information in CS, Section 3.5.2, Table 46, whereby*

the text suggests that the pre-treatment costs are applied as a lump-sum cost in the first model cycle to all patients starting ripretinib or BSC in the PFS state in the first model cycle.

[Answer provided in responses delivered on 30th June 2025]

B28. Executable model, worksheet “Trace (Ripretinib)”, columns V, X and Y. The formulae in column V include BSC costs for patients who are progression-free, but the formulae in columns X and Y exclude BSC costs for patients who have progressed. Please confirm that these are errors and correct the model.

[Answer provided in responses delivered on 30th June 2025]

B29. Worksheet “Trace (Ripretinib)” columns AD:AG and worksheet “Trace (BSC)”, columns AD:AE. The palliative care (palliative resection and palliative radiotherapy) cost for the PF state is based on the half-cycle corrected model trace, but the cost in the PD state is based on the uncorrected trace. This applies to both the ripretinib and BSC traces. Please confirm that these are errors and correct the model.

[Answer provided in responses delivered on 30th June 2025]

B30. Worksheet “Trace (Ripretinib)”, column AB. The formula which calculates the total treatment costs for ripretinib does not include the values in column Y (costs of treatment in PDO_n (BID Dosing)), which leads to the total treatment costs to decrease if the proportion of PD on-treatment patients requiring BID dosing is included in ‘Cost inputs’ cell F24. Please confirm that this is an error and correct the model.

[Answer provided in responses delivered on 30th June 2025]

B31. PRIORITY. Executable model, worksheet “Model Parameters”, cells D51:54. The probabilistic sampling routine does not account for logical ordering of the health states and the sampled utility value for the PD off treatment states can be higher than that for the sampled utility value for the PF states. Ren *et al.* (*Pharmacoeconomics*, 2018, vol. 36[3]) have proposed a method for sampling

ordered parameters, including utility values. Please apply this method in the model using the variance-covariance matrix from the MMRM.

[Answer provided in responses delivered on 30th June 2025]

B32. Executable model, worksheet “Cost Inputs”, cell F127 and H129. The end-of-life care cost in cell H129 does not update when alternative cost sources are selected from the drop-down menu in cell F127. Please correct this error.

[Answer provided in responses delivered on 30th June 2025]

B33. Executable model, worksheets “Trace (Ripretinib)” and “Trace (BSC)”, column C. Each cycle is assumed to be 1/13 years in duration. The calculations in this column assume that there are 52 weeks in a year. However, there are approximately 52.17 weeks in a year. Please correct the model, if possible.

[Answer provided in responses delivered on 30th June 2025]

References

1. Deciphera Pharmaceuticals LLC. Data on File: Kaplan-Meier plots of the counterfactual and the unadjusted (observed) survival times overlaid with the fitted parametric survival models separately for each set of counterfactual OS times. 2025.
2. Deciphera Pharmaceuticals LLC. Data on File: Empirical unsmoothed hazard, smoothed hazard, and the modelled hazards for each set of (counterfactual) Ripretinib 150mg QD survival times. 2025.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments (review of TA881) [ID6496] Updated Base Case Analysis: Addendum to EAG Report Table 2

September 2025

File name	Version	Contains confidential information	Date
ID6496 Ripretinib Updated Base Case Analysis: Addendum to EAG Report Table 2_redacted	1.1	Yes	26 September 2025

Company revised base case

The Company submits this addendum to the company submission for ID6496 to present a revised base case and revised PAS discount. The Company's preferred revised base case now incorporates an adjustment to ripretinib OS to account for the double dosing (BID) that occurred post-progression in INVICTUS. The Company has also submitted an increased simple PAS to the PASLU. Table 1 presents the Company's revised base case, and relevant scenarios, with the previous (original) PAS that was submitted and approved by the PASLU. Table 2 presents the Company's revised base case, and relevant scenarios, with the updated (increased) simple PAS which has been submitted to the PASLU.

Table 1. Summary of EAG's preferred deterministic model results (Ripretinib vs BSC), including revised base case and updated scenarios (Previous PAS)

Analysis	Inc. QALYs	Inc. Costs	ICER (including DM)	DM
Previous PAS discount ()				
Company's previous base case (CS)			£28,836	1.7
Company's previous base case (updated after clarifying questions)			£28,730	1.7
EA1: Correction of errors			£28,703	1.7
EA2: Selection of alternative OS models (ripretinib = BID-unadjusted exponential; BSC = gen. gamma)			£36,321	1.7
EA3: Selection of alternative OS models (ripretinib = BID-adjusted complex gen. gamma with re-censoring, log-logistic; BSC = log-logistic)			£55,113	1.7
Company's revised base case (updated after EAG report; ripretinib = BID-adjusted complex gen. gamma without re-censoring, lognormal; BSC = gen. gamma)			£34,297	1.7
EA4 - EAG preferred (ripretinib = BID-adjusted complex gen. gamma with re-censoring, log-logistic; BSC = gen. gamma)			£52,822	1.7
ASA1: Alternative OS models unadjusted for BID dosing, includes BID dosing costs (60.1%)				
ASA1a: Exponential			£42,414	1.7

Analysis	Inc. QALYs	Inc. Costs	ICER (including DM)	DM
ASA1b: Weibull			£43,807	1.7
ASA1c: Gompertz			£31,457	1.7
ASA1d: Log-normal			£31,868	1.7
ASA1e: Log-logistic			£32,727	1.7
ASA1f: Generalised gamma			£33,296	1.7
ASA1: Alternative OS models unadjusted for BID dosing, includes BID dosing costs (50%)				
ASA1a: Exponential			£41,390	1.7
ASA1b: Weibull			£42,747	1.7
ASA1c: Gompertz			£30,717	1.7
ASA1d: Log-normal			£31,118	1.7
ASA1e: Log-logistic			£31,955	1.7
ASA1f: Generalised gamma			£32,508	1.7
ASA2: Alternative OS models adjusted for BID (with re-censoring), excludes BID dosing costs				
ASA2a: Exponential			£56,572	1.7
ASA2b: Weibull			£72,639	1.7
ASA2c: Gompertz			£73,815	1.7
ASA2d: Log-normal			£48,656	1.7
ASA2e: Log-logistic			£52,822	1.7
ASA2f: Generalised gamma			£72,868	1.7
ASA3: Alternative OS models adjusted for BID (without re-censoring), excludes BID dosing costs				
ASA3a: Exponential			£45,110	1.7
ASA3b: Weibull			£45,589	1.7
ASA3c: Gompertz			£21,813	1.7
ASA3d: Log-normal			£34,297	1.7
ASA3e: Log-logistic			£34,731	1.7
ASA3f: Generalised gamma			£30,149	1.7
ASA4: Alternative TTD models				
ASA4a: Exponential			£52,822	1.7
ASA4b: Weibull			£52,469	1.7
ASA4c: Gompertz			£53,018	1.7
ASA4d: Log-normal			£58,858	1.7
ASA4e: Log-logistic			£61,355	1.7
ASA4f: Generalised gamma			£53,627	1.7
ASA5: Alternative PFS models				
ASA5a: Exponential			£52,493	1.7
ASA5b: Weibull			£52,473	1.7
ASA5c: Gompertz			£52,559	1.7
ASA5d: Log-normal			£52,822	1.7
ASA5e: Log-logistic			£55,031	1.7
ASA5f: Generalised gamma			£52,521	1.7
ASA6: Alternative placebo group switching OS adjustment				
ASA6a: Unadjusted			£219,436	1.2
ASA6b: Two stage adjusted simple without re-censoring			£53,944	1.7
ASA6c: Two stage adjusted complex without re-censoring			£57,494	1.7

Analysis	Inc. QALYs	Inc. Costs	ICER (including DM)	DM
ASA6d: Two stage adjusted complex with re-censoring	■	■	£55,569	1.7
ASA6e: RPSFTM adjusted without re-censoring	■	■	£55,551	1.7
ASA6f: RPSFTM adjusted with re-censoring	■	■	£48,774	1.7
ASA6g: RPSFTM adjusted with common treatment effect relaxed (ki=0.5; Weibull)	■	■	£49,763	1.7
ASA6h: RPSFTM adjusted with common treatment effect relaxed (ki=0.5)	■	■	£65,442	1.7
ASA7: Alternative health state utility values (GRID values)	■	■	£52,342	1.7

ASA - additional sensitivity analysis; BID - twice daily; CS - company's submission; DM - decision modifier; EA - exploratory analysis; EAG - External Assessment Group; gen. gamma - generalised gamma; ICER - incremental cost-effectiveness ratio; Inc. - incremental; OS - overall survival; PFS - progression-free survival; QALY - quality-adjusted life year; RPSFTM - rank-preserving structural failure time model; TTD - time to treatment discontinuation

Table 2. Summary of EAG's preferred deterministic model results (Ripretinib vs BSC), including revised base case and updated scenarios (updated PAS)

Analysis	Inc. QALYs	Inc. Costs	ICER (including DM)	DM
Updated PAS discount (■)				
EA1: Correction of errors	■	■	£24,637	1.7
EA2: Selection of alternative OS models (riporetinib = BID-unadjusted exponential; BSC = gen. gamma)	■	■	£31,052	1.7
EA3: Selection of alternative OS models (riporetinib = BID-adjusted complex gen. gamma with re-censoring, log-logistic; BSC = log-logistic)	■	■	£46,896	1.7
Company's revised base case (updated after EAG report; riporetinib = BID-adjusted complex gen. gamma without recensoring, lognormal; BSC = gen. gamma)	■	■	£29,350	1.7
EA4 - EAG preferred (riporetinib = BID-adjusted complex gen. gamma with re-censoring, log-logistic; BSC = gen. gamma)	■	■	£44,964	1.7
ASA1: Alternative OS models unadjusted for BID dosing, includes BID dosing costs (60.1%)				
ASA1a: Exponential	■	■	£36,196	1.7

Analysis	Inc. QALYs	Inc. Costs	ICER (including DM)	DM
ASA1b: Weibull			£37,371	1.7
ASA1c: Gompertz			£26,964	1.7
ASA1d: Log-normal			£27,310	1.7
ASA1e: Log-logistic			£28,035	1.7
ASA1f: Generalised gamma			£28,513	1.7
ASA1: Alternative OS models unadjusted for BID dosing, includes BID dosing costs (50%)				
ASA1a: Exponential			£35,332	1.7
ASA1b: Weibull			£36,476	1.7
ASA1c: Gompertz			£26,339	1.7
ASA1d: Log-normal			£26,676	1.7
ASA1e: Log-logistic			£27,382	1.7
ASA1f: Generalised gamma			£27,847	1.7
ASA2: Alternative OS models adjusted for BID (with re-censoring), excludes BID dosing costs				
ASA2a: Exponential			£48,123	1.7
ASA2b: Weibull			£61,678	1.7
ASA2c: Gompertz			£62,682	1.7
ASA2d: Log-normal			£41,452	1.7
ASA2e: Log-logistic			£44,964	1.7
ASA2f: Generalised gamma			£61,872	1.7
ASA3: Alternative OS models adjusted for BID (without re-censoring), excludes BID dosing costs				
ASA3a: Exponential			£38,461	1.7
ASA3b: Weibull			£38,865	1.7
ASA3c: Gompertz			£18,835	1.7
ASA3d: Log-normal			£29,350	1.7
ASA3e: Log-logistic			£29,717	1.7
ASA3f: Generalised gamma			£25,856	1.7
ASA4: Alternative TTD models				
ASA4a: Exponential			£44,964	1.7
ASA4b: Weibull			£44,666	1.7
ASA4c: Gompertz			£45,130	1.7
ASA4d: Log-normal			£50,053	1.7
ASA4e: Log-logistic			£52,157	1.7
ASA4f: Generalised gamma			£45,643	1.7
ASA5: Alternative PFS models				
ASA5a: Exponential			£44,693	1.7
ASA5b: Weibull			£44,674	1.7
ASA5c: Gompertz			£44,752	1.7
ASA5d: Log-normal			£44,964	1.7
ASA5e: Log-logistic			£46,820	1.7
ASA5f: Generalised gamma			£44,715	1.7
ASA6: Alternative placebo group switching OS adjustment				
ASA6a: Unadjusted			£185,602	1.2
ASA6b: Two stage adjusted simple without re-censoring			£45,910	1.7
ASA6c: Two stage adjusted complex without re-censoring			£48,904	1.7

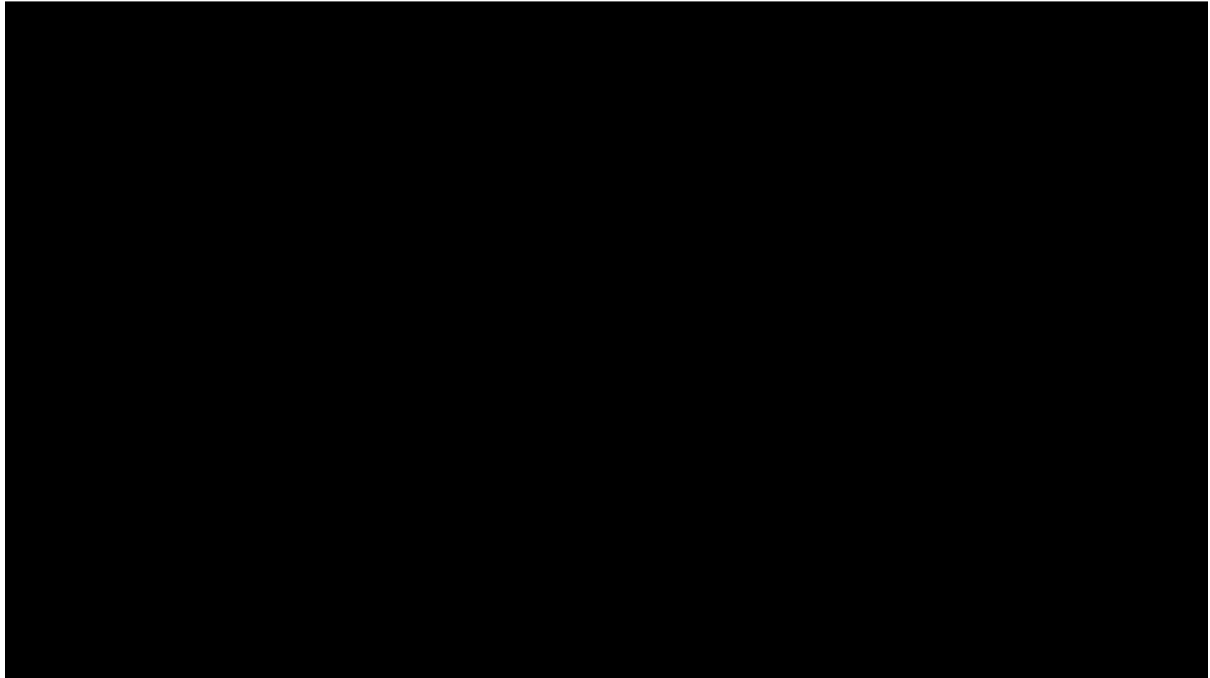
Analysis	Inc. QALYs	Inc. Costs	ICER (including DM)	DM
ASA6d: Two stage adjusted complex with re-censoring	■	■	£47,281	1.7
ASA6e: RPSFTM adjusted without re-censoring	■	■	£47,265	1.7
ASA6f: RPSFTM adjusted with re-censoring	■	■	£41,549	1.7
ASA6g: RPSFTM adjusted with common treatment effect relaxed (ki=0.5; Weibull)	■	■	£23,469	1.7
ASA6h: RPSFTM adjusted with common treatment effect relaxed (ki=0.5)	■	■	£24,152	1.7
ASA7: Alternative health state utility values (GRID values)	■	■	£44,555	1.7

ASA - additional sensitivity analysis; BID - twice daily; CS - company's submission; DM - decision modifier; EA - exploratory analysis; EAG - External Assessment Group; gen. gamma - generalised gamma; ICER - incremental cost-effectiveness ratio; Inc. - incremental; OS - overall survival; PFS - progression-free survival; QALY - quality-adjusted life year; RPSFTM – rank-preserving structural failure time model; TTD – time to treatment discontinuation

Company rationale for revised base case regarding re-censoring

The Company base case prefers a without re-censoring approach whereas the EAG's preferred base case includes a with re-censoring approach. The Company has adopted its position because re-censoring can introduce undue uncertainty when the intention is to extrapolate survival beyond the period of the trial due to loss of data. The company has explored both censoring and non-censoring approaches and notes that TSD24 does not state a preference for either approach. TSD24 states that "The loss of follow up information and the early truncation of the survival curves, due to re-censoring, may have an impact in terms of increased uncertainty when the intention is to extrapolate survival beyond the period of the trial". With re-censoring, survival follow-up for patients receiving ripretinib is much shorter; for example, there are 20 patients left at risk at 87 weeks in the without re-censoring analysis vs 37 weeks in the with re-censoring analysis. Additionally, when plotted as Kaplan-Meier OS curves, the early truncation of the curve is immediately followed by a sharp drop in survival probability, which has a significant impact on the long-term extrapolations, largely driven by a drop in the number of patients at risk (53 to 10) (Figure 1).

Figure 1. Kaplan-Meier plot of time from randomisation to death, subjects randomised to ripretinib QD (N=85). Impact of re-censoring of counterfactual (CF) survival times within two-stage estimation adjustment for IPDE



IPDE – Inpatient dose escalation, post-progression

Single Technology Appraisal
**Ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more
treatments (review of TA881) [ID6496]**

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	[REDACTED]
2. Name of organisation	GIST Cancer UK
3. Job title or position	[REDACTED]
4a. Brief description of the organisation (including who funds it). How many members does it have?	We are a small not for profit Charity solely for GIST patients and their families. We work with patients and their families to support them through diagnosis and treatment phases, through our helpline, information leaflets and patient face to face meetings. We work alongside Sarcoma UK to fund research Funding is through donations from members and their families.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] If so, please state the name of the company, amount, and purpose of funding.	No
4c. Do you have any direct or indirect links	No

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	Through our patient forum, face to face patient meetings and focus groups.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Patients experience GIST and its side effects in diverse ways, with varied responses to treatment. For some, a diagnosis—particularly when the disease has metastasized—signals a terminal condition, necessitating palliative care. Many report profound fatigue, requiring frequent rest and significant lifestyle changes. As a result, some have had to take early retirement or reduce their working hours and daily activities. The mental toll of living with a disease that, while currently managed, carries the constant uncertainty of treatment failure is immense. Alongside fatigue, patients commonly face symptoms such as nausea, stomach cramps, diarrhoea, weight loss, poor appetite, thinning hair, blisters, peeling skin, and foot pain. Even simple outings require extensive planning, ensuring access to toilets, quiet rest areas, and a change of clothing. Carers, despite their unwavering support, often feel helpless. The psychological strain of the disease affects them too—disrupting sleep patterns and burdening them with the same stress as patients. The fact that Regorafenib is the final treatment option further amplifies anxiety, depression, and emotional distress for both patients and their families.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	These firsthand accounts highlight the varied experiences patients have when accessing treatment and care for GIST. While some receive excellent support at specialist centres, others struggle with delayed follow-ups, limited access to expert care, and challenges in securing necessary treatments. It's clear that specialised care can make a significant difference in a patient's journey, from timely monitoring to compassionate support. However, gaps in accessibility and disparities in treatment options can add to the uncertainty and stress. Patients who rely on private insurance may face additional concerns when transitioning to public healthcare systems, particularly with limitations on available medications. One patient said, 'The current treatments that have been available to me so far, (Imatinib, Sunitinib and Regorafenib) have been effective up till now. The care that I receive at The Christie could not be better. I and my family are extremely grateful for this.' Another patient shared, 'My treatment has, thus far, been private. However, since I have now retired, I don't think I can continue as a private patient as it will be seen as a pre-existing condition. I may have access to Ripretinib via private insurance, but I won't under the NHS. That's my major worry as I could be out of options soon'. A third shared 'My treatment and care at a GIST specialist centre, has been excellent, there have been no issues, and the staff have been kind, caring and compassionate. I have been monitored regularly, and the supply of drugs has never been a problem. Overall, superb.' However, anecdotally, many patients that we speak to through our forum do not have such positive experiences. They are not seen at a GIST specialist centre and can find that they do not get timely follow up appointments, feedback from scans and some have been refused transfer of care to a specialist unit.
8. Is there an unmet need for patients with this condition?	The unmet need is for those patients whose treatments no longer work or due to the type of GIST (PDGFRA mutation) are unable to take the 3 available treatments in the UK: Imatinib, Sunitinib and Regorafenib. Any new drug could mean that these people are given a longer life outcome. The data that shows improved response in those patients with Exon17/18 mutations specifically, in addition trial data shows better tolerance (fewer side effects) than Sunitinib or Regorafenib? Patients who have inoperable GIST, have been on all 3 TKIs and these have now stopped working. Patients who are in all other ways healthy and still relatively young are facing a death sentence when the drugs stop working.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	These patient experiences offer a powerful insight into the impact of TKIs for those living with GIST. The ability to take medication at home, maintain a relatively normal lifestyle, and experience fewer side effects than traditional chemotherapy makes these treatments invaluable. However, the unpredictability of their effectiveness and the potential for resistance remain a major concern, especially for patients who have exhausted all available options. It's clear that for many, TKIs provide hope and stability, allowing them to work, care for their families, and contribute to society. But the need for continued research and access to new therapies is urgent, particularly for those facing resistance and limited alternatives. One patient wrote: 'The advantages of these drugs are that as they are targeted therapy, so don't have the extreme side effects that can occur with chemotherapy; they can be taken at home and for me the side effects have been mostly manageable, and the drugs gave me a good quality of life. They were my only hope because my GIST is inoperable.' Another said. 'The advantages are that they are targeted and don't give such severe side-effects as chemotherapy. The disadvantage is that they often don't last that long before the cancers mutate and become resistant.' Another commented, 'The current drug treatments (TKIs) for GIST are hugely valuable to us as patients whatever stage our tumours are at. This is partly because we know that chemotherapy and radiotherapy do not work for GISTs, so without them, many of us would not now be alive. But it is also because TKIs seem to have far fewer and less severe side effects than standard chemo and radiotherapy for other cancers. This means that many of us are able to carry on with most aspects of our pre-GIST lives. There are patients on the forum who have been able to carry on working for many years, bring up children, or contribute to society through other activities, as well as living rewarding lives for themselves with families and friends. The fact that we can take these treatments at home, makes it easier for us and presumably not so costly for the NHS as we don't go to hospital for treatment. I really can't think of any significant disadvantages, other than the side effects, which for many of us are manageable and a small price to pay for our survival.' Another added, 'I'm grateful for the fact that there medications out there for this incurable disease. However, the effectiveness and longevity is unpredictable. Imatinib works well for most mutations and with relatively manageable side effects, this remains the best line against GIST.' The data that shows improved response in those patients with Exon17/18 mutations specifically, in addition trial data shows better tolerance (fewer side effects) than Sunitinib or Regorafenib?

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The frustration of a postcode lottery in treatment availability is a significant challenge for patients who rely on these life-extending therapies. Advocacy for broader access to Ripretinib in the UK could be crucial in ensuring that patients who have exhausted other options are not left without hope. The disadvantage is that there are only 3 of these tyrosine kinase inhibitors (TKIs) available in the NHS - and because GISTs mutate, patients live with the knowledge that their treatment can stop working at any time. I don't know how long sunitinib will work for me but I'm very aware that after this there is currently only one more 'line of defence' in the form of Regorafenib. This is very sobering, particularly when Ripretinib is approved for use in the USA and Europe. It feels a bit like a "postcode lottery" on a worldwide scale at the moment, with the UK being excluded. Having a 4th line of defence (Ripretinib) available, for those of us for whom surgery is not an option, would make an enormous difference and give us hope. After imatinib, the drugs have more significant side effects and, in some cases, become intolerable for some people to continue. Therefore, leading to a shorter life expectancy if patients can't tolerate the side effects. The way in which treatment is delivered requires reviewing. The process of 1st, 2nd, 3rd or 4th line drugs is outdated and unhelpful for the mental and emotional wellbeing of patients. For example, it is proven sunitinib works better for Exon 9 or for mutations 13 and 14. However, Regorafenib works better for people from Exon 11 to mutations 17 and 18. This needs to be considered when prescribing for patients to give them the best outcomes. Considering personalized treatment approaches based on mutation type is also important. The current stepwise approach to TKIs may not always provide the best outcomes, and a more tailored strategy—prescribing drugs based on specific mutations rather than rigid treatment lines—could improve patient survival and quality of life.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The Phase 3 INTRIGUE trial has provided valuable insights into the effectiveness of Ripretinib for patients with KIT exon 11 and exon 17/18 mutations. While the trial initially found that Ripretinib was not superior to Sunitinib in the general patient population, a Circulating Tumour DNA (ctDNA) biomarker analysis revealed that patients with KIT exon 11 and secondary exon 17/18 mutations experienced significantly improved progression-free survival when treated with Ripretinib compared to Sunitinib—14.2 months vs. 1.5 months. This finding is particularly important for patients with inoperable metastatic GISTs, as they have no other treatment options available in the UK once Imatinib, Sunitinib, and Regorafenib have failed. The ability to extend life expectancy through palliative targeted therapies is crucial, especially given the limited availability of Ripretinib in the UK despite its approval in the USA and Europe. A patient commented, ‘Patients with inoperable metastatic GISTs would presumably benefit the most because there are currently no other treatment options available in the UK after imatinib, sunitinib and Regorafenib have failed. A Circulating Tumour DNA (ctDNA) biomarker analysis of the Phase 3 INTRIGUE trial (2024) showed better progression-free survival in response to Ripretinib, than to Sunitinib, in patients with KIT exon 11 and exon 17/18 mutations.’ Another said, ‘It is those of us that are inoperable that can get extended life expectancy from palliative treatment with these targeted therapies. Adjuvant doses following successful surgery, tend to be with Imatinib only, rather than the 1st, 2nd and 3rd line drugs. Another patient added, ‘By the time we get to need a 3rd or 4th line treatment, we have no alternative treatments, and potentially all of us could benefit. Imatinib remains the primary option for adjuvant treatment following surgery while patients requiring third- or fourth-line treatments often face uncertainty and limited alternatives. Expanding access to Ripretinib could provide hope and extended survival for many patients who currently have no further options.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues

13. Are there any other issues that you would like the committee to consider?	We are writing to express deep concern regarding the continued lack of approval for Ripretinib in the UK despite its authorization in the USA and Europe. As a patient advocate, I am deeply troubled by the disparity in treatment options available to individuals with advanced gastrointestinal stromal tumours (GIST) who have exhausted existing tyrosine kinase inhibitors (TKIs). The findings from the Phase 3 INVICTUS and INTRIGUE trials demonstrate Ripretinib's ability to significantly improve progression-free survival (PFS), particularly in patients who have failed at least three prior TKIs. Furthermore, the Expanded Access Programme provided clear evidence that UK patients benefited from this treatment when no other options remained. The median overall survival advantage highlighted in the INVICTUS trial—18.2 months with Ripretinib vs. 6.3 months with placebo—should prompt a reconsideration of NICE's stance. Additionally, patients with exon 11 KIT mutations have been shown to have significantly better progression-free survival outcomes with Ripretinib. Given this data, NICE should consider not only approving Ripretinib as a fourth-line treatment but also exploring its earlier use for exon 11 patients where appropriate. A crucial factor in treatment decisions should not solely be survival but also quality of life. Compared to sunitinib, Ripretinib presents a far more favourable safety profile, reducing the incidence of severe adverse events such as neutropenia, hand-foot syndrome, and hypertension. The ability for patients to continue living independently, maintaining their mobility and overall well-being, must be a priority in determining cost-effectiveness. While the financial implications of drug approval are important, patients rightfully question how committees evaluate the worth of a life when such treatments could significantly extend survival and maintain quality of life. Given the limited number of eligible patients in the UK, the overall budget impact of approving Ripretinib would be manageable. We urge NICE to reconsider its position on Ripretinib, ensuring UK patients have equitable access to treatment options already available internationally. Advanced GIST patients deserve evidence-based care that maximizes their survival potential and quality of life, rather than being left without viable alternatives when current TKIs fail. These patient perspectives highlight the deep frustration and hope surrounding the approval of Ripretinib in the UK. While the drug has already been authorized in the USA and Europe, the NHS and NICE's hesitance to approve it creates a significant gap in treatment options for those with advanced, inoperable GIST who have exhausted other TKIs. The findings from Phase 3 INVICTUS and INTRIGUE trials clearly demonstrate Ripretinib ability to improve progression-free survival, particularly for patients who have failed at least three prior TKIs. The Expanded

	Access Programme, which provided Ripretinib to UK patients with disease progression, also suggests that many benefited from its availability. The question many patients are asking is: why was this international trial data sufficient for approval in other regions but not the UK? The cost of Ripretinib remains a major barrier—\$32,000 per month is difficult to justify under NHS budgets. However, patients rightly question how a committee evaluates the worth of a life when such treatments could significantly extend survival and maintain quality of life for those who currently have no other options. Beyond the financial concerns, there's also an urgent need for treatment personalization—rather than rigid 1st, 2nd, 3rd, and 4th line drug sequences, prescribing based on mutation type could provide better outcomes for individual patients. These voices matter in shaping policy decisions. A patient said, 'As I understand it, Ripretinib was approved by the US Food & Drug Administration (FDA) in 2020 and by the European Medicines Agency in 2021, for the treatment of patients with advanced GIST who have already had treatment with at least 3 TKIs. Approval was based on the findings of the Phase 3 INVICTUS clinical trial, a double-blind, randomised, placebo-controlled study, which showed a statistically significant improvement in progression-free survival with Ripretinib, in GIST patients who had received prior treatment with 3 or more TKIs. Following this trial, an international Expanded Access Programme was initiated to provide Ripretinib to UK patients who had disease progression after at least 2 lines of approved therapies. In the INTRIGUE trial comparing Ripretinib with sunitinib (2024) the safety profile was consistently more favourable for Ripretinib.' A further commented, 'In the light of these findings, I very much hope that NICE will feel able to recommend the use of Ripretinib in the NHS to allow patients access to the most appropriate evidence-based care, which can prolong their lives and give hope to them and their loved ones.' Another patient said, 'This appraisal will assess the clinical and cost effectiveness of Ripretinib. Last time I checked the cost of Ripretinib was \$32,000 per month. In all honesty, the life of any of us would not be seen, by the taxpayer, to be worth that amount. What criteria will the "committee" use to assess the worth of a person's life?' Another commented, 'Ripretinib has been approved for use in the USA and Europe, using the same trial data that led to NICE previously not approving it for use in the UK. This seems very strange and unfair to us as patients in the UK. It makes the NHS an outlier and suggests something went wrong in the first appraisal. Surely the NHS would want to be offering treatment that is in line with Europe and the US.'

A further comment, 'There should always be new drugs being trailed and hopefully available to all when approved by NICE. Keep fighting, living a full life and stay positive as there are new and innovative ways to treat cancer.'

Ripretinib is not only offering another treatment level but also a more effective treatment for some GIST types post Imatinib.

A final comment, 'Due to the varying types of GIST, not all of the current available treatments work for patients, therefore it is important for patients to have all known affective treatments available to them to have the best quality of life with loved ones whilst living with this incurable disease.' 'On a separate note, I would also like to add it would be beneficial for once a patient is diagnosed with GIST, it is mandatory that the patient gets referred to a GIST specialist.'

We would also point out that the numbers likely to benefit from Ripretinib if approved would be small so costs would be limited.

Patients with GISTs harbouring *KIT* exon 9 mutation benefit more from sunitinib than do those with exon 11 mutation, because Sunitinib is better at targeting this *KIT*-independent oncogenic pathway activation. Ripretinib on the other hand has a different mechanism of action and can overcome all known primary mutations and secondary mutations associated with GIST progression and imatinib resistance, especially those in *KIT* exons 13, 14, 17, and 18. This is particularly relevant for Exon 11 patients, where secondary mutations are a much more common cause of imatinib resistance.

In the INVICTUS trial, Ripretinib significantly improved mPFS in 129 patients with advanced or metastatic GISTs, including those with *KIT* and *PDGFRA* mutations that progressed following treatment with imatinib (first-line therapy), sunitinib (second-line therapy), regorafenib (fourth-line therapy and beyond) and/or other drugs relative to placebo (6.3 months vs 1.0 month, $P < 0.0001$). Ripretinib significantly prolonged the median OS (18.2 months vs 6.3 months) in this population. But, in the INTRIGUE study, patients with advanced GISTs who had been treated with imatinib received 6 weeks of Ripretinib or sunitinib as a second-line therapy. The median PFS was similar between the Ripretinib and sunitinib groups (8.0 and 8.3 months, respectively).

	However, looking deeper into this data, among patients with exon 11 <i>KIT</i> mutations, the mPFS was better in the Ripretinib group (n = 163, 72.12%) than in the sunitinib group (n = 164, 72.25%; 8.3 months vs 7.0 months, HR 0.88, <i>P</i> = 0.36)/ Importantly, the incidence of treatment-emergent adverse events (AEs) of grade ≥ 3 was significantly lower with Ripretinib than with sunitinib (24% vs 51%). Compared with the sunitinib group, the Ripretinib group experienced significantly fewer grades 3 and 4 treatment-emergent AEs (65.6% vs 41.3%), specifically neutropenia (6.3% vs 0%), hand-foot syndrome (10.0% vs 1.3%), and hypertension (26.7% vs 8.5%), and significantly fewer AEs such as diarrhoea and fatigue. There are two issues- one is whether NICE should fund Ripretinib as a fourth line therapy for everyone who's run out of other options; two is whether NICE should fund it earlier in treatment for specific patients with exon 11 mutations. 1. After the three licenced TKIs there are no further treatment options in the UK, and this is out of line with treatment offers in Europe and USA. Whilst Ripretinib is not necessarily better than sunitinib head-to-head in the INTRIGUE trial, If you don't have sunitinib anymore because you've become resistant to it, INVICTUS shows that Ripretinib works well. The median overall survival was 18.2 months versus just 6.3 in the patients who got nothing. If they are going to fund 3 lines of treatment, what on earth justification do they have for stopping arbitrarily at the fourth when it's shown to prolong life? 2. Overall, Ripretinib can as much as triple overall survival in advanced or metastatic GIST according to Invictus; INTRIGUE was less convincing but certainly showed no harm in ripritenib over sunitinib. Importantly, it has a much better side effect profile so that people can get on with their lives whilst on treatment- hand and foot syndrome is awful to live with and means people can't walk/type/support themselves, which has a major cost to society 3. In exon 11 patients Ripretinib significantly improves progression free survival in all the major trials. Within this, patients with KIT exon 11 mutations and exon 17/18 secondary mutations had 9 times better overall survival with Ripretinib. At the very least NICE should fund Ripritenib in exon 11 patients.

14. Are treatments used in previous lines used after progression on those treatments?	

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission.	• Enable <u>all</u> patients to receive treatment no matter what stage their GIST Cancer is. • Ensure that rare cancers are given equal access to drugs and treatment across the UK (Rare Cancers Bill currently in Parliament). • In exon 11 patients Ripretinib significantly improves progression free survival in all the major trials. • Ripretinib not only offering another treatment level but also a more effective treatment for some GIST types • End the postcode lottery for this drug which has been proven effective in clinical trials and is used across the world.

Thank you for your time.

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Single Technology Appraisal

Ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments (review of TA881) [ID6496]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	[REDACTED]
2. Name of organisation	PAWS-GIST
3. Job title or position	[REDACTED]
4a. Brief description of the organisation (including who funds it). How many members does it have?	PAWS-GIST is a consortium of specialist GIST doctors and patient advocates focused on improving care and stimulating research to find improved treatments for Paediatric, Adolescent, Wild-type and Syndromic GIST patients. We run a specialist clinic in Cambridge which is the first of its kind in Europe and second of its kind in the world. We are funded with grant funding and charitable donations by patients their families & well-wishers. We are not a membership organisation but consist a core team of GIST specialists and patient advocates amounting to 8-10 in number. Our clinic manages c. 30 new PAWS-GIST patient cases each year. Cumulatively our clinic engages with several hundred PAWS-GIST patients representing the largest grouping of this rare cancer outside of America.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] If so, please state the name of the company,	PAWS-GIST has received no funding from Deciphera who are bringing Ripretinib to NICE for evaluation.

amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	I have been gathering information first-hand about the experiences of GIST patients and carers since my daughter was diagnosed with this cancer in 2010. During the past 15 years I have engaged with many hundreds of patients both in the UK and internationally while operating as a GIST patient advocate. My work to find answers has naturally allowed me to engage with GIST patients, clinicians and researchers world-wide and collaborating with specialists such as Dr Ramesh Bulusu and Professor Andy Hall I am the co-founder of the National GIST Tissue bank and the PAWS-GIST clinic which are to support research efforts to find a cure for all forms of GIST cancer. I participate in private GIST patient forums and social media platforms which offer support to patients and host three PAWS-GIST clinics each year which are attended by patients and their families who care for them, so have an expert first-hand understanding about the experiences of patients and carers. I have seen evidence of Ripretinib trials presented at GIST conferences in Europe, USA & UK. Here it has been described as having a favourable safety profile, along with significantly improved progression-free survival results in GIST patients previously treated with all approved therapies. I have interviewed a selection of GIST patients using ripretinib.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	GIST cancer is a Sarcoma which differs in many ways from the more commonly understood carcinoma cancers. Treatment often involves surgery in addition to tablets taken orally rather than chemotherapy administered intravenously. Those GIST patients who are fortunate enough to be diagnosed very early while it is possible to surgically remove all of the tumour before it has spread, can go on to lead cancer free lives under surveillance. While a GIST cancer diagnosis is a terrible shock to patients and their families complete surgical removal is the best outcome aside from the negative impact on their mental health of a cancer diagnosis. For those GIST patients whose disease has already metastasized (spread to other parts of the body) at diagnosis or whose disease returns after surgery the focus and all of their hopes rely upon the existence of drugs that will stop / slow the growth of the tumour(s) and enable them to continue living. Luckily the first, second- and third-line drugs that are available to GIST patients are very effective for the more commonly found GIST mutations and as a result many patients are able to “live with GIST cancer” and continue their lives as they have done previously as regards to studying, working and engaging with their families and in society. There are undoubtedly side effects with all of the therapies but with guidance from oncologists, specialist nurses and other patients these are in the main manageable. Carers experience significant stress and distress watching the person they love battling to survive and searching for treatments that will target their type of GIST. Seeing other GIST patients respond to treatments designed specifically to target the mutation driving their GIST cancer makes the drive to seek effective treatments for a loved ones’ type of GIST even greater. Being a rare cancer, GIST patient carers often find themselves very involved in advocating for the patient to ensure they are receiving the best treatment available. Being a GIST cancer patient or carer is not a way of life that anyone would choose.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	GIST patients and their families are hugely grateful for the treatments and care available on the NHS. There are designated specialist centres who are expert in the care of GIST patients. These specialists work as part of a multidisciplinary team consisting: <u>Surgeons</u> - GIST surgery requires specialist experience to achieve the best outcome <u>Oncologists</u> – experienced in understanding which treatments will be suited to the individual patients’ unique circumstances. <u>Pathologists</u> – who can identify the specific type(s) of GIST to advise the oncologists regarding targeted therapies. <u>Radiologists</u> – Who can from the outset recognise a mass as possible GIST. <u>Specialist Nurses</u> – Who help and support patients navigate their treatment journey and manage physical and mental side effects. We all recognise and value the dedication and expertise delivered by the NHS clinicians and feel very fortunate that this service is available GIST cancer patients in the UK.
8. Is there an unmet need for patients with this condition?	Yes, there is an unmet need for those patients whose GIST cancer is inoperable at diagnosis, whose disease returns after surgery or grows beyond the reach of the first, second- and third-line drugs that are currently available in England.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	The patients we have interviewed have cited the following advantages of Ripretinib: • Tumour shrinkage • Manageable side effects • Oral administration at home • Minimal detrimental effect on quality of life • A 4th line treatment option which can prolong life and the hope of a further more effective / curative option.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The main disadvantage flagged by patients and carers is knowing that Ripretinib is effective as a fourth line treatment but not being able to access it. Living with the knowledge that a third line treatment can stop working and that there are no further approved treatment options is terrifying. Side effects such as loss of hair and sore feet are perfectly acceptable compared to the alternative.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The GIST patients who will benefit most from Ripretinib are patients with inoperable GIST whose disease has progressed beyond the control of the first, second- and third-line therapies currently available. GIST tumour progression happens because the tumour(s) develop mutations which are resistant to the current treatment. Ripretinib has been designed to target these specific resistance mutations.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	The main equality issue is that Ripretinib is available to GIST patients in other parts of the world e.g. in Europe, America, Australia but is not yet available to patients in the UK.

Other issues

13. Are there any other issues that you would like the committee to consider?	No
14. Are treatments used in previous lines used after progression on those treatments?	We understand that, unless a patient is unable to tolerate a treatment that until a further TKI treatment is available to a GIST patient, it is standard practice to keep the patient on treatment. Although there may be progression the current TKI will still have some effect on controlling the disease until the next treatment is accessible. The aim is to avoid “tumour flare” caused by the active drug brakes being taken off completely leaving nothing to contain/slow the tumour growth.

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission.	Ripretinib: • Inhibits the mutations that are resistant to first, second- and third-line GIST therapies. • Has a manageable side effect profile • Is taken orally • Is life extending – allowing time to access further specifically targeted treatment options • Will provide treatment equality for UK GIST patients.

Thank you for your time.

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Single Technology Appraisal

Ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments (review of TA881) [ID6496]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	[REDACTED]
2. Name of organisation	Sarcoma UK
3. Job title or position	[REDACTED]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Sarcoma UK is registered as a charity in England and Wales (1139869) and in Scotland (SC044260); and as a company limited by guarantee in England and Wales (7487432). We are a national charity that funds vital research, offers support for anyone affected by sarcoma cancer and campaigns for better treatments, and the only cancer charity in the UK focusing on all types of sarcoma. The vast majority of our funding comes from donations and legacies. We currently employ 35 staff.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] If so, please state the name of the company, amount, and purpose of funding.	Sarcoma UK has not received any funding from Deciphera Pharmaceuticals in the last twelve months. However, we may receive a funding contribution up to £3,000 in the coming months from Deciphera which would go towards the costs of the charity hosting two Sarcoma Community Days in June and September respectively. These focus on well-being, peer support and education, for adult patients and their supporters. We have not received any funding in the last twelve months from Novartis, Pfizer or Bayer, which have developed the existing three-lines of treatment for GISTs, Imatinib, Sunitinib and Regorafenib.
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	We do not have any direct or indirect links with, or funding from, the tobacco industry.

5. How did you gather information about the experiences of patients and carers to include in your submission?	We have used four main evidence sources: (1) Sarcoma UK runs a Support Line which has received over 28,700 contacts with over 6,070 individuals since 2016. It receives daily phone and email enquiries, including regular contact from GIST patients. (2) We maintain contact with specialist sarcoma centres and designated treatment centres in all four nations of the UK to understand current treatment options and patient experience, through our Support Line and Policy and Public Affairs function, and by hosting two meetings a year of the Chairs of the Sarcoma Advisory Group within regional Cancer Alliances. These oversee Sarcoma MDTs which deliver care and treatment in in Sarcoma Specialist Centres and by designated practitioners in Local Sarcoma Units. (3) Every five-years we run a National Sarcoma Survey which gathers quantitative evidence about the experiences of people affected by sarcoma, in terms of sarcoma as a health condition, diagnosis and NHS care and treatment. This includes Adult Patients (16+), Parents of Under-16s, and Family and Carers. Our 2020 survey received over 1,117 responses, including 87 adults diagnosed with a GIST (14%) and 18 (5%) from carers or family members. Our 2025 survey report (to be published in July) received 1,024 responses, including 43 (6%) adults diagnosed with a GIST and 5 (2%) were carers or family members. (4) In June 2025, we will publish our <i>State of the Nation review of sarcoma services and treatment</i>, the largest qualitative study of its kind ever undertaken in the UK. This received 323 responses from patients and carers across all four nations (198 and 16 from people in England and Wales respectively); and 61 responses from healthcare professionals, researchers, government department, NHS organisations or charities across the four nations, between October 2024 to January 2025. • 84 responses were from a patient with a GIST, a carer or family member • 24 GIST patients stated they had been given Imatinib, Sunitinib or Regorafenib (the existing three treatment lines, see Q7 below). Some patients reported they were effective; whilst others reported they had significant side-effects, had to be given reduced doses, or had to discontinue treatment. • One GIST patient reported that they had been given access to Ripretinib on compassionate grounds (having become resistant to Regorafenib), but did not comment further about Ripretinib.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	GISTs are the most common soft tissue sarcoma. An average of 795 cases of GIST are diagnosed every year in England. GIST makes up 20.16% of all soft tissue sarcomas, about 0.26% of all cancers. They develop in the gastrointestinal (GI) tract which runs from the oesophagus to the anus and includes the stomach and intestines. Most GISTs are found in the stomach and small bowel but can occur anywhere along the GI tract. The median age at diagnosis is 68 years old (Sarcoma UK, Gastrointestinal stromal tumour (GIST)). • An analysis of people diagnosed with one of 84 soft tissue sarcoma sub-types in England between 2013 and 2017, found that people diagnosed with GIST in England have a 5-year survival of 86%. (Source: Andrew Bacon, Kwok Wong, Malee S. Fernando, Brian Rous, Roger J. W. Hill, Shane D. Collins, John Broggio, Sandra J. Strauss, Incidence and survival of soft tissue sarcoma in England between 2013 and 2017, an analysis from the National Cancer Registration and Analysis Service (December 2022). • GIST symptoms vary depending on the tumour's size and location. They may include blood in your poo or vomit; anaemia; fatigue; fever and sweating at night; discomfort or pain in your stomach; painless lump in the stomach; feeling sick and vomiting; or weight loss. The most common symptoms and side effects reported by GIST patients to our 2020 and 2025 <i>National Sarcoma Surveys</i>, were: fatigue, diarrhoea, changes to hair, skin and nails, nausea or vomiting. Fatigue has the greatest impact on their lives, during and after treatment. • Many GIST respondents to our National Sarcoma Surveys reported that diagnosis and treatment negatively affected their overall mental health/ wellbeing: 48% in 2020 and 50% in 2025 said "to some extent"; 9% in 2020 and 24% in 2025 said "severely". 40% of GIST respondents in 2020 and over 50% in 2025, said they would have liked to have received more emotional support from hospital staff during their treatment. • GIST patients, overall, manage to work whilst managing treatment side effects. In both surveys, according to carers, around half of patients either often, sometimes, or always have trouble taking care of themselves. Living with a GIST can mean relying on loved ones, impacting mentally, financially and socially on patients and carers. Carers provide patients with emotional support; accompany them on trips and appointments; transport and travel with the patient; and may communicate on their behalf. Carer respondents to both surveys spent between a few hours or up to at least 35 hours a week giving care and support. Over half of carers had to stop working or studying, either temporarily or permanently. 71% of carers in 2020 and 100% in 2025 said they had experienced a negative financial impact due to a patient's sarcoma diagnosis. At least 80% of carers said they had felt either more often or constantly depressed or anxious since the diagnosis.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Three main treatment-lines exist for GIST patients with advanced disease. (1) Imatinib is effective for around 80% of patients and on average will control the disease for about two years. (2) Sunitinib is used if the tumour becomes resistant to imatinib. (3) Regorafenib is used if a GIST cannot be operated on, has become metastatic, the patient has already received Imatinib and Sunitinib but it has not worked or has had bad side effects. • Some treatments are more or less effective dependent on mutations within the tumour. The efficacy of different treatments also partly depends on the age of the patient, any co-morbidities, and if they can tolerate side-effects. Imatinib is considered to be the most-effective. Sunitinib and Regorafenib can also be effective for some patients; but compared to Imatinib, may have diminishing results generally and are more toxic. For a very small handful of patients with Neurotrophic Tyrosine Receptor Kinase (NTRK) positive tumours including sarcomas, Larotrectinib was approved in England under the Cancer Drugs Fund in 2020. • However, there is a significant population who do not have an effective treatment because the treatment does not target their mutation, or progression renders the treatment ineffective. It is common for GIST patients to stop responding to treatments as they develop resistance after a certain length of time. Of the 24 GIST patients who responded to our <i>State of the Nation</i> review that said they had received Imatinib, Sunitinib or Regorafenib: some said they were effective; others said they had significant side-effects, had to be given reduced doses, or had to discontinue treatment on them. One respondent received Ripretinib on compassionate grounds after becoming resistant to Regorafenib. • NHS England (NHSE) aims to have 75% of all cancers diagnosed at stages I or II by 2028. However, it is difficult to understand the stage at which sarcoma patients are diagnosed as there is incomplete data for sarcoma – on average just over 50% of sarcomas had staging data reported over the four quarters of 2024 (NHS England, National Disease Registration Service, (2024)). Many respondents to our <i>State of the Nation</i> review, including GIST-patients, received a late diagnosis, often having to see their GP or another health professional multiple times before receiving an onward referral for further scans or assessment. • NHS England's Sarcoma Service Specification stipulates that <u>all</u> GIST patients should be treated by a specialist sarcoma cancer team; but only 64% of GIST respondents in 2020 and 61% in 2025 to our national surveys, said this was the case. Many GIST-patients that responded to our <i>State of the Nation</i> review reported difficulties in getting the correct referral to a sarcoma specialist centre. Another national charity told us that many GIST patients are unaware that they should be treated in a specialist centre and could only rely on the advice given by healthcare professionals as they have little or no awareness of the current referral pathway. • 42% of GIST respondents to our 2020 <i>National Sarcoma Survey</i> (and 50% in 2025 to our Survey), said they were not given any information at diagnosis. 51% in 2020 and 57% in 2025 had a named clinical nurse specialist. Many said that diagnosis and treatment negatively their overall mental wellbeing: 48% in 2020 and

	50% in 2025 said “to some extent”; 9% in 2020 and 24% in 2025 said “severely”. 40% of GIST respondents in 2020 and over 50% in 2025, said they would have liked to have received more emotional support from hospital staff during their treatment. Many GIST respondents to our <i>State of the Nation review</i> highlighted struggling from mental distress due to a diagnosis but were offered little or no support for their mental health.
8. Is there an unmet need for patients with this condition?	• There is a significant population who do not have an effective treatment either because the treatment does not target their mutation, or progression renders the treatment ineffective. It is common for GIST patients to stop responding to treatments as they develop resistance after a certain length of time. Of the 24 GIST patients that responded to our <i>State of the Nation review</i>, who stated they had received Imatinib, Sunitinib or Regorafenib: some said they were effective; others that they had significant side-effects, had to be given reduced doses, or had to discontinue treatment on them. One respondent received Ripretinib on compassionate grounds after becoming resistant to Regorafenib. • There are no other treatments for GIST patients beyond three lines of therapy, after which patients have on average six weeks of life remaining. Patients are frustrated by a lack of effective treatment options for GISTs, and the treatment options available often have severe side-effects, leading many to require a lower (and less effective) dose. Therefore, there is a continuing and ongoing unmet need in this population. • This ongoing unmet need for GIST patients, is symptomatic of inadequate support for research into sarcomas, including GIST, which was highlighted by patients and healthcare professionals that responded to our <i>State of the Nation review</i>. It is clear that the development of a wider range of new treatments, is due to systemic barriers, due to market failure (i.e. lack of profitability), lack of funding, lack of clinical trials or inequitable access to those that are being run, which hold back the development of new treatments.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	GIST-patients make clear that having access to an increased number of kinder, more effective therapies would be welcomed, especially as there are currently no treatments for this group of patients after three lines of therapy. Studies have shown that following these three treatments, patients have on average six weeks of life remaining. • Clinical trials indicate that Ripretinib has key advantages for GIST patients in terms of its efficacy as a treatment and in having a significantly reduced side-effect profile compared to other lines of treatment. This is significant in terms of being able to extend life beyond the existing three lines of treatment and providing relatively improved quality of life. <u>The Invictus trial reported that Ripretinib “significantly improved median progression-free survival compared with placebo and had an acceptable safety profile in patients with advanced [GISTs] who were resistant to approved treatments.”</u> (Source: Prof Jean-Yves Blay, Prof Michael C Heinrich, Prof John Zalcborg, Sebastian Bauer, Prof Hans Gelderblom, Prof Patrick Schöffski, Robin L Jones, Steven Attia, Gina D'Amato, Ping Chi, Peter Reichardt, Julie Meade, Kelvin Shi, Rodrigo Ruiz-Soto, Suzanne George, Prof Margaret von Mehren, <i>Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial</i> (July 2020). • A further study investigated Ripretinib's efficacy and safety in a group of 45 patients in the UK. <u>Its “results show that both the efficacy and the safety of ripretinib in this group of patients were comparable to what had been reported in available clinical trials, supporting its use in patients with advanced [GISTs].”</u> (Source: Su Yin Lim, Laura Ferro-López, Elizabeth Barquin, Daniel Lindsay, Khin Thway, Myles J. Smith, Charlotte Benson, Robin L. Jones, Andrea Napolitano, <i>Efficacy and Safety of Ripretinib in Advanced Gastrointestinal Stromal Tumors within an Expanded Access Program: A Cohort Study</i>, (February 2024). • Key symptoms that Ripretinib may help to mitigate that GIST patients reported to our 2020 and 2025 <i>National Sarcoma Surveys</i> include: fatigue; diarrhoea; changes to hair, skin and nails; and nausea or vomiting. GIST patients said that fatigue was the side effect with the greatest impact on their life, both during and after treatment. As well as the significant impact on mental wellbeing following a diagnosis and treatment. • For carers and other family members, Ripretinib may potentially extend a GIST patients' life after three lines of therapy. This may help to mitigate some of the practical and emotional impacts upon carers and family members, compared to the current position, as studies have shown that following these three treatments, patients have on average six weeks of life remaining. Second, living with GIST has a major impact on the patient's quality of life, and the side-effects of existing treatments for the condition are significant; which in turn places a high physical and emotional burden on family and carers. Allowing access to Ripretinib may reduce the physical and emotional burden on family and carers to some extent.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The current first three lines of treatment for GIST patients - Imatinib, Sunitinib and Regorafenib - can be more or less effective dependent on mutations within the tumour. However, there is a significant population who do not have an effective treatment either because the treatment does not target their mutation, or progression renders the treatment ineffective. Further to this, it is common for patients to stop responding to treatments. And there are currently no treatments for GIST patients after three lines of therapy. Studies have shown that following these three treatments, patients have on average six weeks of life remaining. By comparison, Sarcoma UK is not aware of Ripretinib having any disadvantages compared to the above current standard treatments, as we understand that it may: (a) Potentially extend patients' lives after three lines of therapy with reduced side-effects compared to having on average only six weeks of life remaining. (b) Provide an improved quality of life by mitigating: - (i) Some of the physical symptoms experienced by GIST patients, including fatigue which has the greatest impact, both during and after treatment, as reported to our 2020 and 2025 <i>National Sarcoma Surveys</i>. As well as other reported symptoms of diarrhoea; changes to hair, skin and nails; and nausea or vomiting. (ii) The impact on mental wellbeing, following a diagnosis and treatment. (c) Extend patients' lives, reduce side-effects and improve quality of life, it may also mitigate the physical and emotional burden on family and carers.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	For people with GISTs, there are currently no treatments after three lines of therapy. Studies have shown that following these three treatments, patients have on average six weeks of life remaining. Patients are frustrated by a lack of effective treatment options for GISTs, and the treatment options available often have severe side-effects, leading many to require a lower (and less effective) dose. Therefore, there is a continuing and ongoing unmet need in this population. This ongoing unmet need for GIST patients, is symptomatic of inadequate support for research into sarcomas, including GIST, which was highlighted by both patients and healthcare professionals that responded to our <i>State of the Nation review</i>. It is clear that the development of a wider range of new treatments, is due to systemic barriers, due to market failure (i.e. lack of profitability), lack of funding, lack of clinical trials or inequitable access to those that are being run, which hold back the development of new treatments.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Yes, there are health inequalities issues that need to be considered which affect GIST patients, which are avoidable, unfair and systematic differences in health between different groups of people, including socio-economic factors. • Analysis of routinely collected NHS data shows that social deprivation has an impact on survival. GIST patients in England diagnosed from 2013-2017 in the fifth deprivation quintile were 24% more likely to die of their disease than those in the least deprived group ($p < 0.1$, weak evidence). The same trend is seen with greater significance across all soft tissue sarcomas, and the findings for sarcomas appear more pronounced than for more common cancers. • There was also an increasing likelihood for patients to present through an emergency route as deprivation increases; although cases of soft tissue sarcoma were less common in more deprived areas for male patients. (Source: Andrew Bacon, Kwok Wong, Malee S. Fernando, Brian Rous, Roger J. W. Hill, Shane D. Collins, John Broggio, Sandra J. Strauss, Incidence and survival of soft tissue sarcoma in England between 2013 and 2017, an analysis from the National Cancer Registration and Analysis Service, (December 2022). GIST patients are also affected by health inequalities related to how the NHS responds to their needs: • Whilst NHSE aims to have 75% of all cancers diagnosed at stages I or II by 2028; it is difficult to understand the stage at which sarcoma patients are diagnosed as there is incomplete data for sarcoma – on average just over 50% of sarcomas had staging data reported over the four quarters of 2024 (NHS England, National Disease Registration Service, (2024)). Many respondents to our <i>State of the Nation</i> review, including GIST-patients, received a late diagnosis, often having to see their GP or another health professional multiple times before receiving an onward referral for further scans or assessment. • NHS England's Sarcoma Service Specification stipulates that <u>all</u> GIST patients should be treated by a specialist sarcoma cancer team; but only 64% of GIST respondents in 2020 and 61% in 2025 to our national surveys, said this was the case. Similarly, many people with GISTs that responded to our <i>State of the Nation</i> review, often reported difficulties in getting the correct referral to a sarcoma specialist centre. Another national charity also told us that many GIST patients are often unaware that they should be treated in a specialist centre and could only rely on the advice given by healthcare professionals as they have little or no awareness of the current referral pathway.

Other issues

13. Are there any other issues that you would like the committee to consider?	N/A
14. Are treatments used in previous lines used after progression on those treatments?	Yes, treatments used in previous lines can be used after progression on those treatments. Rechallenge with imatinib is considered an option in patients with advanced GISTs, following progression with the three main lines of treatment, Imatinib, Sunitinib and Regorafenib. For example, a study from Italy of a total of 104 eligible advanced GIST patients, previously treated with Imatinib, Sunitinib and Regorafenib, were collected from six referral Italian institutions. The study explained: <i>“Overall, 71 patients treated with imatinib 400 mg as rechallenge were included. Mutational status was available in all patients. The median follow up was 13 months. In patients who received a rechallenge therapy, the median time to progression (TTP) was 5.4 months [95% confidence interval (CI) 1.9–13.5] and overall survival (OS) was 10.6 months (95% CI 2.8–26.9). A correlation between mutational status, response rate, TTP and OS was not found but comparing deleted versus nondeleted KIT exon 11 patients, a significant difference was identified in terms of TTP and OS ($p = 0.04$ and $p = 0.02$, respectively).”</i> The study concluded that, <i>“imatinib rechallenge is a reasonable option in advanced GIST. The prognostic value of the specific KIT mutations was confirmed in our series.”</i> It also went on to state <i>“that imatinib rechallenge is widely used in Italian clinical practice and that it positively affects patient outcome, with an OS (10.6 months) and TTP (5.4 months) advantage superior to that observed in other studies. Therefore, imatinib rechallenge should be offered to all patients after failure of previous treatments.”</i> (Source: Vincenzi B, Nannini M, Badalamenti G, Grignani G, Fumagalli E, Gasperoni S, D'Ambrosio L, Incorvaia L, Stellato M, Spalato Ceruso M, Napolitano A, Valeri S, Santini D, Tonini G, Casali PG, Dei Tos AP, Pantaleo MA. Imatinib rechallenge in patients with advanced gastrointestinal stromal tumors following progression with imatinib, sunitinib and regorafenib, Ther Adv Med Oncol, (August 2018).)

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission.	• For people diagnosed with a GIST, fatigue has the biggest impact, during and after treatment. As well as other reported symptoms of diarrhoea; changes to hair, skin and nails; and nausea or vomiting. 48% of GIST respondents in 2020 and 50% in 2025 to our <i>National Sarcoma Surveys</i> said, their mental wellbeing was impacted “to some extent”; 9% in 2020 and 24% in 2025 said “severely”. • GIST patients work whilst dealing with treatment side effects; but according to carers in both surveys, around half of patients either often, sometimes, or always have trouble taking care of themselves. Carers may have to stop working or studying and have elevated levels of depression or anxiety following the diagnosis. • No effective treatments exist for many GIST-patients as they do not target their mutation. Current treatments have severe side-effects – so patients may require a lower and less effective dose. They may stop responding to treatment as resistance grows over time, or progression of the disease renders treatment ineffective. Patients are frustrated by a lack of effective treatment options after three lines of therapy; after which they may have on average six weeks of life remaining. There is a continuing and ongoing unmet need for many GIST patients in this population. People in the fifth deprivation quintile are almost 25% more likely to die of their disease than those in the least deprived group. • Ripretinib’s benefits: potentially extending GIST patients’ lives after three lines of therapy with reduced side-effects compared to only on average only six weeks of life remaining. And provide a better quality of life by mitigating symptoms experienced by GIST patients, during and after treatment, including fatigue which has the greatest impact, both during and after treatment. Extending patients’ lives, reduced side-effects and improved quality of life, may mitigate the physical and emotional burden on family and carers.

Thank you for your time.

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Single Technology Appraisal

Ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments (review of TA881) [ID6496]

Clinical expert statement

Information on completing this form

In [part 1](#) we are asking for your views on this technology. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

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Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Clinical expert statement

Ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments (review of TA881) [ID6496]

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

The deadline for your response is **5pm** on **<insert deadline>**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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Part 1: Treating gastrointestinal stromal tumours and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Charlotte Benson
2. Name of organisation	Royal Marsden Hospital
3. Job title or position	Consultant Medical Oncologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with gastrointestinal stromal tumours? ☐ A specialist in the clinical evidence base for gastrointestinal stromal tumours or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	N/A
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for gastrointestinal stromal tumours (For example, to stop progression, to	The main aim in localised GIST is cure with surgery and sometimes the addition of imatinib in the adjuvant and/or neoadjuvant setting.

Clinical expert statement

Ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments (review of TA881) [ID6496]

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improve mobility, to cure the condition, or prevent progression or disability)	In recurrent or metastatic GIST the aim is to stop disease progression, improve overall survival, improve disease related symptoms and maintain quality of life
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Reduction in tumour size and or density/enhancement on serial CT/MRI imaging Reduction/ stabilisation of uptake on a FDG PET scan Stabilisation of a growing tumour and/or modification of rate of growth Symptomatic benefit- improvement in disease related symptoms Maintenance of quality of life/ability to perform daily tasks
10. In your view, is there an unmet need for patients and healthcare professionals in treating gastrointestinal stromal tumours?	Yes there is an unmet need for patients with GIST that are progressing after 3 or more lines of therapy. There is also inequality when compared to GIST patients in Europe and around the world
11. How are gastrointestinal stromal tumours currently treated in the NHS? - Are any clinical guidelines used in the treatment of the condition, and if so, which? - Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) - What impact would the technology have on the current pathway of care?	GISTs in the UK are treated according to NICE Guidelines and also with reference to British Sarcoma Group GIST guidelines (https://pubmed.ncbi.nlm.nih.gov/38840030) and ESMO GIST guidelines (https://pubmed.ncbi.nlm.nih.gov/34560242/) and Sarcoma Advisory Group guidance. The pathway of care for patients is well defined following implementation NICE Improving Outcome Guidelines that state patients with Sarcoma/GIST are referred to and discussed at specialist sarcoma centres. This refers to most patients with GIST although some are still not referred to specialist centres. The standard treatment paradigm for patients with recurrent or metastatic GIST is well defined with imatinib, sunitinib and regorafenib treatment. Sunitinib and regorafenib are less well tolerated drugs with significant side effect profiles, particularly regarding cardiovascular side effects which can make these treatments difficult to tolerate and hard to maintain the optimal dosing needed for tumour control. Therefore, some patients with pre-existing cardiovascular disease may not be able to receive or tolerate these treatments at the best anti tumour dose. The option of Ripretinib after 3 or more treatments would make a significant difference in terms of treatment options as the only other option is supportive

Clinical expert statement

Ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments (review of TA881) [ID6496]

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	care. Due to earlier diagnosis of patients with GIST and increasing knowledge about available treatments and improvement in side effect managements, this group of later line patients are increasingly fit and well, often working and functioning within society and deserve the best available treatment. Given the very active research landscape in GIST with several new drugs in development maintaining patients on Ripretinib will also allow patients access to future clinical trials as they arise.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? - How does healthcare resource use differ between the technology and current care? - In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) - What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Ripretinib would be given in an outpatient setting identical to that which is already set up for patients with GIST seen at specialist oncology centres. i.e. outpatient monitoring with regular blood tests, clinical reviews and cross-sectional imaging with specialist medical and nursing support liaising directly with primary care as required There is no new investment that is needed
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? - Do you expect the technology to increase length of life more than current care? - Do you expect the technology to increase health-related quality of life more than current care?	Yes
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Yes Mutational analysis of KIT gene has allowed us to pinpoint those patients who are most likely to benefit from ripretinib. Increasingly we perform biopsies (or sometimes surgery) in patients with metastatic disease and often have information about KIT mutational status and development of resistance

Clinical expert statement

	mutations which allows us to refine treatment choices, allowing precision medicine. There is also the option of utilising circulating tumour DNA (ctDNA) analysis looking for presence of resistance mutations in the blood. Exploratory analysis of ctDNA in patients taking part in the Phase 3 Intrigue trial has shown the patients with Exon 17/18 mutations in particular benefit from ripretinib (https://pubmed.ncbi.nlm.nih.gov/38182785/) and there is a worldwide clinical trial in progress currently recruiting in the UK and elsewhere to explore this further (Clinical trial reference NCT05734105) In addition, as ripretinib has a better cardiovascular safety profile than sunitinib and regorafenib. Therefore this drug is a good option for patients that have progressed through both sunitinib/regorafenib due to poor tolerance of cardiovascular side effects or difficulty achieving a therapeutic dose and thus control of GIST
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	The side effect profile of ripretinib is similar to other tyrosine kinase inhibitors and GIST specialists and specialist nurses are already familiar with managing these in routine practice. No additional monitoring tests will be needed
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Starting treatment with ripretinib will follow the usual treatment rules in a GIST setting. That is disease progression on existing treatment which is defined as clinically significant increase in tumour size/enhancement on serial imaging in conjunction with worsening disease-related symptoms. This will also take in to account tolerability of existing treatment/side effect management. Stopping rules in a 4th and likely last line setting are related to clinical benefit and or evidence of significant symptomatic disease progression.

Clinical expert statement

	This will not require additional testing over and above routine clinical practice
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Yes- improvement in disease control and disease related symptoms coupled with a reasonable side effect profile of ripretinib will translate in to good quality of life
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? - Is the technology a 'step-change' in the management of the condition? - Does the use of the technology address any particular unmet need of the patient population?	Yes Ripretinib meets an unmet need in patients in the 4th line setting or beyond who currently have no other treatment options available to them. The current use of regorafenib in the 3rd line is associated with significant difficulties maintaining a clinically therapeutic dose given its side effect profile. Given the ongoing rapid expansion of new agents currently undergoing early phase clinical trials in GIST the option of ripretinib to maintain clinical response will also open up future treatment options for patients in later line settings.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effects are manageable with patient education and input from GIST clinicians and specialist nurses
20. Do the clinical trials on the technology reflect current UK clinical practice? - If not, how could the results be extrapolated to the UK setting? - What, in your view, are the most important outcomes, and were they measured in the trials?	Yes they do Patients taking part in the INVICTUS clinical trial of ripretinib versus placebo were performance status 0-2 (https://pubmed.ncbi.nlm.nih.gov/32511981/) which would be the same as those seen in clinical practice The primary outcome measure of progression free survival was met (6.3 months versus 1.0 month) with a median overall survival of 15.1 months versus 6.6 in

Clinical expert statement

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	the placebo group. Dose reductions of ripretinib and discontinuation was low (6% and 5% respectively) which demonstrate the tolerability of ripretinib with a clinically relevant difference in quality of life scores. I am not aware of other adverse effects and have not come across additional effects in my clinical practice.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	I have had direct clinical experience of many patients receiving ripretinib as part of an expanded access scheme. There have been approximately 60 patients treated at my hospital. Ripretinib is well tolerated in this population of patients who are largely performance status 1-2. In addition, patients have had prolonged clinical benefit remaining on treatment for a long period of time with maintained quality of life
22. How do data on real-world experience compare with the trial data?	Please see above
23. NICE considers whether there are any equality issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could	Lack of access of UK patients to this technology which is widely available in Europe and elsewhere

Clinical expert statement

Ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments (review of TA881) [ID6496]

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- exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation
- lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population
- lead to recommendations that have an adverse impact on disabled people.

Please consider whether these issues are different from issues with current care and why.

More information on how NICE deals with equalities issues can be found in the [NICE equality scheme](#).

[Find more general information about the Equality Act and equalities issues here.](#)

Clinical expert statement

Ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments (review of TA881) [ID6496]

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Ripretinib:

- Inhibits the mutations that are resistant to first, second- and third-line GIST therapies.
- Has a manageable side effect profile with few significant cardiovascular effects
- Is taken orally
- Is life extending – allowing time to access further specifically targeted treatment options
 - Will provide treatment equality for UK GIST patients

Thank you for your time.

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Clinical expert statement

Ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments (review of TA881) [ID6496]

Single Technology Appraisal

Ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments (review of TA881) [ID6496]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

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Patient expert statement

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Part 1: Living with this condition or caring for a patient with gastrointestinal stromal tumours

Table 1 About you, gastrointestinal stromal tumours current treatments and equality

1. Your name	Jayne Bressington
2. Are you (please tick all that apply)	☐ A patient with gastrointestinal stromal tumours? ☐ A patient with experience of the treatment being evaluated? ☒ A carer of a patient with gastrointestinal stromal tumours? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	PAWS-GIST
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and do not wish to complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and do not wish to complete this statement ☒ I agree with it and will be completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences).

Patient expert statement

	Please specify what other experience: I have engaged with patients who have direct experience of using Ripretinib, having been fortunate enough to access it in a clinical trial. ☒ I have completed part 2 of the statement after attending the expert engagement teleconference ☐ I have completed part 2 of the statement but was not able to attend the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with gastrointestinal stromal tumours? If you are a carer (for someone with gastrointestinal stromal tumours) please share your experience of caring for them	I have been a carer since my daughter Eve was diagnosed with Gastrointestinal stromal Tumour (GIST) in 2010. During the past 15 years I have engaged with many hundreds of patients both in the UK and internationally while operating as a GIST patient advocate. During the years caring for Eve, I watched her endure many horrific procedures, all aimed at beating this terrible disease. It often felt too much to bear. The initial diagnosis was earth shattering, having to break the news to my child that she had cancer was horrific. Years of standing by, feeling totally helpless and hopeless when; she had to have her stomach removed, emergency races to hospital with anaemia, the ravages of treatments, all of these traumas put enormous strain on Eve and our loving family and friends. Our sole focus was to find an effective treatment that would allow her to survive and thrive. Eve was very a very talented girl who would have achieved great things had her life not been so cruelly cut short. She did everything possible to not let GIST cancer get in her way. There is a huge gap in our lives that she should be filling. What we experienced was a situation where the available drugs did not work for Eve's type of GIST. Unlike other GIST patients who can access drugs that have

Patient expert statement

	been designed to target and shrink / manage the types of GIST tumours that they have, we were not so fortunate as drugs for her type of GIST have not yet been found. My work to find treatments for my daughter has naturally enabled me to engage with GIST patients, clinicians and researchers world-wide and collaborating with specialists such as Dr Ramesh Bulusu and Professor Andy Hall. I am the co-founder of the National GIST Tissue bank and the PAWS-GIST clinic which are to support research efforts to find a cure for all forms of GIST cancer. I participate in private GIST patient forums and social media platforms which offer support to patients and host three PAWS-GIST clinics each year which are attended by patients and their families who care for them, so have an expert first-hand understanding about the experiences of patients and carers and often provide support to patients and carers based on my own first-hand experience. I have seen evidence of Ripretinib trials presented at GIST conferences in Europe, USA & UK. Here it has been described as having a favourable safety profile, along with significantly improved progression-free survival results in GIST patients previously treated with all approved therapies. I have engaged with GIST patients who have been fortunate to access ripretinib to gather information about their experiences.
7a. What do you think of the current treatments and care available for gastrointestinal stromal tumours on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	To answer both of these questions at once, the current treatments that are available for GIST on the NHS consist of Surgery, Imatinib, Sunitinib and Regorafenib (and for NTRK fusion GISTs Larotrectinib and Entrectinib). Everyone is very grateful that these treatments exist and are available as they enable a significant number of GIST patients to live GIST cancer free (<i>if the surgery is successful</i>) or with GIST that is manageable with drug therapy.

Patient expert statement

	The guidance and centralisation of specialist care for GIST in Sarcoma and GIST centres is hugely beneficial as it means that the clinicians treating patients are very familiar with GIST and the optimum way to address them. My only sadness is that there are treatments such as Avapritinib and Ripretinib which have both shown significant efficacy for GIST patients with specific types of mutations but which are not currently available to those that would benefit and as a result their lives come to a premature end.
8. If there are disadvantages for patients of current NHS treatments for gastrointestinal stromal tumours (for example, how they are given or taken, side effects of treatment, and any others) please describe these	All drug therapies for all conditions come with side effects. Not all patients experience side effects. It varies from person to person as each patient is unique as are their responses to drug therapies. The current drug therapies for GIST are taken orally as tablets and most patients generally carry on their normal life living with GIST self-administering the treatments rather than having to go to hospital for them to be administered. The more common side-effects experienced by patients taking NHS treatments can be nausea, diarrhoea, skin rashes, sore hands and feet. All of these are manageable and for most considered a small price to pay for their cancer to be under control.
9a. If there are advantages of ripretinib over current treatments on the NHS, please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does ripretinib help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	9a. I understand from talking to patients who have used Ripretinib that the side effects they have experienced are far less than with both Sunitinib and Regorafenib which are the second and third-line GIST treatments. As a result, most are able to continue working or enjoying a full retirement which is considered advantageous. 9c. There are patients who have disease progression on the first, second and third line therapies who have then experienced extended periods where their tumours have shrunk or stabilised while using Ripretinib. One such patient participated in the last NICE appraisal. Ripretinib was effective for her over a four-year period during which time she was able to enjoy seeing her sons lives progress and welcome two grandchildren into the world, precious times for her and her family. All patients described any side effects as being manageable.

Patient expert statement

10. If there are disadvantages of ripretinib over current treatments on the NHS please describe these. For example, are there any risks with ripretinib If you are concerned about any potential side effects you have heard about, please describe them and explain why	The main disadvantage is knowing that Ripretinib is effective as a fourth line treatment but not being able to access it. Living with the knowledge that a third line treatment can stop working and that there are no further approved treatment options is terrifying. Side effects such as loss of hair and sore feet are perfectly acceptable compared to the alternative.
11. Are there any groups of patients who might benefit more from ripretinib or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	None that I am aware of.
12. Are there any potential equality issues that should be taken into account when considering gastrointestinal stromal tumours and ripretinib? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	I do not know of any equality issues other than the fact that patients in England do not currently have access to Ripretinib whereas patients in Scotland, Europe America and Australia do.

Patient expert statement

13. Are there any other issues that you would like the committee to consider?

No

Patient expert statement

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

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Patient expert statement

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Part 1: Living with this condition or caring for a patient with gastrointestinal stromal tumours

Table 1 About you, gastrointestinal stromal tumours current treatments and equality

1. Your name	Fiona Newton
2. Are you (please tick all that apply)	☒ A patient with gastrointestinal stromal tumours? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with gastrointestinal stromal tumours? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	GIST Cancer UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and do not wish to complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and do not wish to complete this statement ☒ I agree with it and will be completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

Patient expert statement

	☐ I have completed part 2 of the statement after attending the expert engagement teleconference ☒ I have completed part 2 of the statement but was not able to attend the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with gastrointestinal stromal tumours? If you are a carer (for someone with gastrointestinal stromal tumours) please share your experience of caring for them	I was initially diagnosed with a gastrointestinal stromal tumour (GIST) in 2014 after collapsing on holiday with internal bleeding. I underwent a major operation to remove the tumour from my duodenum, followed by 3 years of adjuvant drug therapy with Imatinib. During my time on Imatinib my only significant side effect was fatigue, so I was able to continue working part time in the NHS and look after my children who were 7 and 11 at the time of diagnosis. Unfortunately, in 2019 the GIST returned, this time to my liver, and I underwent another major operation. Although the operation was successful, the GIST returned to one of my ribs 6 months later, and so I was put back on Imatinib indefinitely. As well as the drug therapy, the last 5 years have seen 2 further operations and 6 weeks of radiotherapy which have all taken their toll, physically and mentally, but I was able to sustain a fairly normal life continuing to work part-time, look after my family, and do things that I enjoy like walking, eating out, going to shows and concerts, and going on holiday. Imatinib has been the key stone in my survival over the last 10 years, but sadly this has now stopped working for me, as my GIST has mutated to Exon 17 and is no longer sensitive to the drug. I am now taking part in a clinical trial for a 2nd line drug and will then continue onto Sunitinib and Regorafenib in due course. This has been really difficult to cope with mentally as the clinical trial has uncertain outcomes by its very nature, and Sunitinib is not particularly effective against Exon 17. I could therefore potentially be in an extremely life limiting situation. Ripretinib offers real hope for a patient in my situation because it is proven to be effective against my particular mutation and it is documented to be well tolerated, which would preserve my quality of life, possibly for a year or more which is a huge difference when you are living with terminal illness. It is my dearest wish to see my daughter graduate from university in 3 years – hope is what keeps me going.

Patient expert statement

7a. What do you think of the current treatments and care available for gastrointestinal stromal tumours on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	Imatinib has been a wonderful treatment as it is given me many years of quality life with very few side effects. At present, once Imatinib has stopped working there are two further TKI drugs (Sunitinib and Regorafenib) that are available on the NHS as 2nd and 3rd line treatments. Knowing that these two drugs are available gave me and my family great reassurance when I was on Imatinib, as we knew there were other options once Imatinib stopped working for me, so it wouldn't be the end of the line. However, I know that these further treatments have more significant toxicities and I have recently found out that Sunitinib is not very effect against Exon 17. This means there is really only one life extending option open to me once I have finished the clinical trial - Regorafenib. This is extremely worrying, and living with such high degrees of uncertainty for my future is very upsetting for both me and my family. I would say my views on the current treatments are fairly typical of other GIST patients that I have come into contact with.
8. If there are disadvantages for patients of current NHS treatments for gastrointestinal stromal tumours (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Sunitinib which is the current 2nd line treatment has considerable toxicities and side effects which many patients find challenging. Alongside fatigue and puffy eyes, patients commonly face symptoms such as nausea, stomach cramps, diarrhoea, weight loss, poor appetite, thinning hair, blisters, peeling skin, and foot pain. Often this results in patients having a break from the medication or taking a reduced dose. Patients can also experience biological intolerances to any of the TKI drugs such as damage to kidney or liver function which means that they cannot continue on the medication. In these instances, patients will go straight on to the next drug, so they are not getting the clinical benefit of three separate rounds of drugs. Similarly for patients like me, who have Exon 17 mutation, Sunitinib is simply not effective against the disease. Again, this means that Regorafenib is the currently the only life extending option. This can be a terrifying thought, for me and my family.
9a. If there are advantages of Ripretinib over current treatments on the NHS, please describe these. For example, the effect on your quality of life, your ability	The real advantage of Ripretinib is that it is a tried and tested drug with proven efficacy, particularly against Exon 17/18 mutations. It is also shown to be well tolerated by patients giving them a much better quality of life. Ripretinib offers the chance of a level of certainty in a very uncertain time, in terms of "quality" survival of

Patient expert statement

to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does Ripretinib help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	possibly more than a year. This provides great hope for a longer healthier future and would have a real positive impact on mine and my family's mental health. The most important advantage is that this quality time will enable a patient to prepare themselves and their family for the inevitable. It is a time where last wishes can be fulfilled, time with loved ones savoured, and practical matters sorted whilst experiencing a good quality of life. Ripretinib will help to address the disadvantages of Sunitinib in terms of much improved side effects and also because it has proven efficacy against Exon 17/18.
10. If there are disadvantages of ripretinib over current treatments on the NHS please describe these. For example, are there any risks with ripretinib If you are concerned about any potential side effects you have heard about, please describe them and explain why	The only disadvantage that comes to mind, is that one of the possible side effects of Ripretinib is hair loss which the other TKIs don't tend to exhibit. This I feel would be a very small price to pay for extended quality of life with my family.
11. Are there any groups of patients who might benefit more from ripretinib or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	As explained previously, Ripretinib will be of particular benefit for patients like me with Exon 17/18 mutations as it has proven efficacy. It will also be of great benefit for patients who have not been able to tolerate one of the previous drugs.
12. Are there any potential equality issues that should be taken into account when considering gastrointestinal stromal tumours and ripretinib? Please explain if you think any groups of people with this condition are particularly disadvantage	GIST is a rare cancer and there are not often breakthroughs in treatment of the scale you see for some of the more common cancer types. It can sometimes feel like we are forgotten about, so the chance to have access to a new drug that is proven to extend life, and good quality of life, feels like the opportunity to redress some of this imbalance. Many GISTers continue to contribute to society through work and raising family whilst on treatment and this could be further enabled by access to Ripretinib. It is a real beacon of hope.

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Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	No

Patient expert statement

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Ripretinib is particularly effective for GIST patients with Exon 17/18 mutations.
- Ripretinib is well tolerated by patients in terms of side effects and biological toxicities.
- Ripretinib will in some cases be a vital 2nd or 3rd line treatment if other TKIs have failed to work or are intolerable.
- Ripretinib offers a level of certainty for an extended period of 'quality' life in which valuable preparations can be made.
- GIST is rare with few breakthroughs – access to Ripretinib would help to redress the inequality of treatment options.

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**Ripretinib for treating advanced gastrointestinal stromal tumours after 3
or more treatments (review of TA881) [ID6496]**

External Assessment Group report

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Paul Tappenden led the assessment. Ruth Wong critiqued the company's search strategy. Munira Essat and Katy Cooper summarised and critiqued the clinical effectiveness data reported within the company's submission. Jen-Yu Amy Chang and Kate Ren critiqued the statistical aspects of the submission. Paul Tappenden, Aline Navega Biz and Andrew Rawdin critiqued the health economic analysis submitted by the company and conducted additional exploratory analyses. All authors were involved in drafting and commenting on the final report.

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Abbreviations

4L	Fourth-line
4L+	Fourth- and subsequent-line
AE	Adverse event
AF	Acceleration factor
AFT	Accelerated failure time
AIC	Akaike Information Criterion
ASA	Additional sensitivity analysis
ASCO	American Society of Clinical Oncology
BIC	Bayesian Information Criterion
BICR	Blinded independent central review
BID	Twice daily (<i>bis in diem</i>)
BNF	British National Formulary
BSC	Best supportive care
CASP	Critical Appraisal Skills Programme
CDA-AMC	Canada's Drug Agency L'Agence des médicaments du Canada
CDSR	Cochrane Database of Systematic Reviews
CEAC	Cost-effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CMU	Commercial Medicines Unit
CR	Complete response
CS	Company's submission
CSR	Clinical Study Report
CT	Computed tomography
cuSCC	Cutaneous squamous cell carcinoma
DARE	Database of Abstracts of Reviews of Effects
DCO	Data cut-off
DM	Decision modifier
DoR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EA	Exploratory analysis
EAG	External Assessment Group
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-item
EQ-5D	Euroqol 5-Dimensions
EQ-5D-5L	Euroqol 5-Dimensions 5-Level
ERG	Evidence Review Group
ESMO	European Society of Medical Oncology
FAC	Factual accuracy check

FBC	Full blood count
GI	Gastrointestinal
GIST	Gastrointestinal stromal tumour
HCHS	Hospital and Community Health Services
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
Inc.	Incremental
IPCW	Inverse probability of censoring weights
IPD	Individual patient data
IPDE	Intra-patient dose escalation
IQR	Interquartile range
IRR	Independent radiological review
ITC	Indirect treatment comparison
ITT	Intention-to-treat
LFT	Liver function test
LSM	Least squares mean
LY	Life year
LYG	Life year gained
MCID	Minimal clinically important difference
MHRA	Medicines and Healthcare products Regulatory Agency
MMRM	Mixed model for repeat measures
MRI	Magnetic resonance imaging
MUGA	Multiple gated acquisition
N	Number
N/a	Not applicable
NCCN	National Comprehensive Cancer Network
NE	Not evaluable
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NHSCII	NHS Cost Inflation Index
NICE	National Institute for Health and Care Excellence
NR	Not reported
ONS	Office for National Statistics
OS	Overall survival
PAS	Patient Access Scheme
PBAC	Pharmaceutical Benefits Advisory Committee
PD	Progressed disease
PDGFRA	Platelet derived growth factor receptor alpha
PF	Progression-free
PFS	Progression-free survival
PH	Proportional hazards
PPES	Palmar-plantar erythrodysaesthesia syndrome

PRO	Patient-reported outcome
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QD	Once daily (<i>quaque die</i>)
Q-Q	Quantile-quantile
RCS	Restricted cubic spline
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria In Solid Tumours
RPSFTM	Rank-preserving structural failure time model
RT	Radiotherapy
RWE	Real-world evidence
SAE	Serious adverse event
SCC	Squamous cell carcinoma
SD	Stable disease <i>or</i> Standard deviation
SE	Standard error
SF-6D	Short Form 6-Dimensions
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
TA	Technology Appraisal
TBP	Treatment beyond progression
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
TSD	Technical Support Document
TTD	Time to treatment discontinuation
TTP	Time to progression
TUDD	Time until definitive deterioration
UK	United Kingdom
US	United States
VAS	Visual analogue scale
WTP	Willingness-to-pay

1. EXECUTIVE SUMMARY

This report assesses ripretinib for the treatment of advanced gastrointestinal stromal tumours (GISTs) after at least three prior treatments, including imatinib. This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision-making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.5 explain the key issues in more detail. The results of the EAG's preferred analysis are summarised in Section 1.6. Background information on the condition, technology and evidence and information on non-key issues are detailed in the [main EAG report](#).

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

The key issues identified by the EAG are summarised in Table 1.

Table 1: Summary of the EAG's key issues

ID3805	Summary of issue	Report sections
Issue 1	Concerns regarding the exclusion of a later data-cut of INVICTUS from the company's model	4.3.5, critical appraisal point 2
Issue 2	Uncertainty surrounding the long-term benefits of ripretinib on OS, including the effects of BID dosing	4.3.5, critical appraisal points 3 and 5
Issue 3	Inconsistency between the health outcomes and costs associated with BID dosing in the company's model	4.3.5, critical appraisal point 4

EAG - External Assessment Group; OS - overall survival; BID - twice daily

The company's economic model is informed by analyses of overall survival (OS) data from the INVICTUS trial (in which some patients dose-escalated to ripretinib 150mg twice daily [BID] after disease progression) but includes the costs of ripretinib 150mg once daily (QD) dosing only. The key difference between the company's base case model and the EAG's preferred analysis relates to how OS is modelled. The company's model applies log-logistic distributions fitted to OS data which have been adjusted for treatment switching in the best supportive care (BSC) group and OS data which have not been adjusted for the effects of BID dosing in the ripretinib group. The EAG's preferred model includes adjustment of the ripretinib OS data to remove the effects of BID dosing using the two-stage estimation method and applies a log-logistic model fitted to the BID-adjusted OS data. The EAG's preferred model also applies a generalised gamma distribution to the switching-adjusted OS data in the BSC group.

1.2 Overview of key model outcomes

NICE technology appraisals (TAs) compare how much a new technology improves length of life (OS) and health-related quality of life (HRQoL) in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Compared with BSC alone, ripretinib is assumed to impact on QALYs by:

- Extending progression-free survival (PFS)
- Extending OS
- Slightly reducing HRQoL due to a higher burden of adverse events (AEs).

Compared with BSC alone, ripretinib is assumed to affect costs by:

- Increasing overall costs due to the acquisition cost of ripretinib (including use of the drug after disease progression)
- Increasing overall disease management costs due to extended OS
- Increasing the costs associated with managing AEs.

The modelling assumptions that have the greatest effect on the ICER for ripretinib versus BSC are:

- Whether OS data in the ripretinib group are adjusted to account for the effect of post-progression ripretinib 150mg BID dosing in the INVICTUS trial. Adjustment using the two-stage estimation method with re-censoring leads to higher ICERs compared with the equivalent adjustment models excluding re-censoring.
- The choice of parametric survival model fitted to the adjusted/unadjusted ripretinib OS data.
- Whether the OS data in the BSC group are adjusted to account for confounding due to treatment switching in the placebo group of INVICTUS.

1.3 The decision problem: Summary of the EAG's key issues

The company's submission (CS) describes the current treatment pathway for patients with advanced GIST as being comprised of first-line imatinib, second-line sunitinib, third-line regorafenib and BSC. The evidence in the CS relates to the clinical effectiveness and cost-effectiveness of fourth- and subsequent-line (4L+) ripretinib (plus BSC) versus BSC alone for the treatment of patients with advanced GIST. The decision problem addressed in the CS is generally in line with the final NICE scope. The value proposition presented in the CS reflects the use of ripretinib within its marketing authorisation i.e., at a dose of 150mg once daily (QD). However, the CS also presents an economic scenario analysis in which the costs of BID dosing are included.

In the previous NICE appraisal of ripretinib for GIST (TA881), clinical advisors to the Evidence Review Group (ERG) explained that a large proportion (50% or more) of patients who receive third-line regorafenib continue to receive this treatment after progression. The clinical advisors commented that if ripretinib was recommended for use in the NHS, they would discontinue regorafenib at the point of

progression; this indicates that continued post-progression regorafenib may be considered as a relevant comparator for ripretinib. However, in this previous appraisal, the company concluded that insufficient data exist to inform a reliable indirect treatment comparison (ITC). The EAG believes that data to inform this ITC are still lacking.

1.4 The clinical effectiveness evidence: Summary of the EAG's key issues

The CS presents data from the INVICTUS randomised controlled trial (RCT) of ripretinib 150mg QD (once a day) plus BSC versus placebo plus BSC in 129 patients with advanced GIST who had progressed on, or were intolerant to, (at least) imatinib, sunitinib and regorafenib. Upon progression, patients randomised to ripretinib could discontinue ripretinib, continue their current dose of 150mg QD, or double their dose to 150mg BID, whilst patients randomised to placebo who progressed could discontinue the study or switch to ripretinib 150mg QD. At the May 2019 data cut-off (DCO), median PFS was 6.3 months for ripretinib versus 1.0 months for placebo (hazard ratio [HR] 0.15, 95% confidence interval [CI] 0.09 to 0.25, $p < 0.0001$). Median OS was 15.1 months for ripretinib versus 6.6 months for placebo (HR 0.36, 95% CI 0.21 to 0.62, $p = \text{not reported [NR]}$), 11.6 months in placebo crossover patients, and 1.8 months in placebo non-crossover patients. At the January 2021 DCO, the most common Grade 3/4 treatment-emergent adverse events (TEAEs) with ripretinib (vs. placebo) were: anaemia (11% vs. 14%); abdominal pain (7% vs. 5%); hypertension (7% vs. 0%); increased lipase (5% vs. 0%) and hypophosphataemia (5% vs. 0%). At the May 2019 DCO, treatment-related Grade 3/4 TEAEs were reported in ■■■ of patients in the ripretinib arm and ■■■ of patients in the placebo arm. TEAEs of special interest included squamous cell carcinoma (SCC) of the skin ■■■■■■■■■■ and actinic keratosis ■■■■■■■■■■.

The EAG's clinical advisors considered the population of enrolled in INVICTUS to be broadly representative of those who would be seen in NHS practice. At the factual accuracy check (FAC) stage of the appraisal, the company clarified that its proposed positioning of ripretinib is as a fourth- and subsequent-line (4L+) therapy, which is aligned with the patient population enrolled in INVICTUS.

The clinical evidence presented in the CS also includes Real World Evidence (RWE) from the Royal Marsden expanded access cohort study of ripretinib for treating GIST. Forty-two percent of patients included in this study had received only two prior lines of treatment before initiating ripretinib. As this is not consistent with the licensed indication for ripretinib, these patients fall outside the scope of the appraisal. This limits the relevance of this study.

1.5 The cost-effectiveness evidence: Summary of the EAG's key issues

The company's economic model assesses the cost-effectiveness of ripretinib plus BSC versus BSC alone for the 4L+ treatment of patients with advanced GIST. The model adopts a partitioned survival approach which includes four health states: (i) progression-free; (ii) progressed disease (on treatment);

(iii) progressed disease (off treatment/BSC), and (iv) dead. The analysis adopts an NHS and Personal Social Services (PSS) perspective, including QALYs accrued by GIST patients; caregiver effects are not included. Clinical outcomes for both treatment groups are based on parametric survival models fitted to data on PFS and OS from INVICTUS, including adjustment of OS in the BSC group to account for treatment switching which occurred in the placebo arm of the trial. The company's base case analysis applies the costs of ripretinib 150mg QD dosing only and does not include any statistical adjustment of OS in the ripretinib group to account for the effects of post-progression ripretinib 150mg BID dose escalation on OS in the intervention arm of the trial. Health state utility values are based on Euroqol 5-Dimensions 5-Level (EQ-5D-5L) data from INVICTUS (mapped to the 3-level version) based on a mixed model for repeat measures (MMRM) analysis. Resource use and cost parameters were taken from a clinical expert survey used in NICE TA488, standard costing sources and other literature.

A Patient Access Scheme (PAS) has been proposed for ripretinib; this takes the form of a simple price discount of [REDACTED] (PAS price = [REDACTED] for 30 days' supply). All ICERs presented in this EAG report include this PAS. The company's base case model applies a decision modifier of 1.7 which is consistent with estimates obtained from the York QALY Shortfall Calculator. Following the clarification round, the company submitted a revised version of the model which included the correction of errors and additional functionality to address several issues raised in the EAG's clarification letter. The probabilistic version of the company's updated model suggests that compared with BSC, ripretinib generates an additional [REDACTED] QALYs at an additional cost of [REDACTED]; including the decision modifier of 1.7, the ICER is expected to be £28,576 per QALY gained. The deterministic version of the model suggests a slightly higher ICER of £28,730 per QALY gained.

The EAG critically appraised the company's health economic analysis and double-programmed the deterministic version of the company's original model. The EAG also checked the amendments applied in the company's updated model. The EAG's critical appraisal identified three key issues: the exclusion of a later data-cut of OS from INVICTUS from the company's model ([Issue 1](#)); uncertainty surrounding the long-term benefits of ripretinib on OS, including the effects of BID dosing ([Issue 2](#)), and inconsistency between the health outcomes and costs associated with BID dosing in the company's model ([Issue 3](#)).

Issue 1: Concerns regarding the exclusion of a later data-cut of INVICTUS from the company's model

Report section	4.3.5 critical appraisal point 2
Description of issue and why the EAG has identified it as important	The data on time to treatment discontinuation (TTD), PFS and OS used in the company's model reflect the 15 th January 2021 DCO of INVICTUS. This is the same DCO used in the economic model used to inform TA881. The company's clarification response explains that there is a later data-cut for OS and safety in INVICTUS from May 2022, but that these data were not included in the economic model. This later data-cut would have provided approximately 16 months of additional follow-up compared with the January 2021 DCO. The exclusion of these data is a limitation of the model which unnecessarily increases uncertainty around the effect of ripretinib on OS.
What alternative approach has the EAG suggested?	The EAG believes that the company should have applied the latest DCO for OS, with appropriate statistical adjustments, as this would have provided additional information to inform long-term predictions of OS for ripretinib. However, this would be a substantial undertaking as it would require the company to repeat all of the analyses of the OS data using the later data-cut, including: (i) the statistical adjustment of OS to account for treatment switching in the placebo arm; (ii) the statistical adjustment of OS to account for intra-patient dose escalation (IPDE) to 150mg ripretinib BID dosing in the ripretinib arm (applied in the company's scenario analyses only) and (iii) updating all parametric survival models fitted to the adjusted OS data in both treatment groups.
What is the expected effect on the cost-effectiveness estimates?	The impact of using the updated data-cut for OS on the ICER for ripretinib is unclear.
What additional evidence or analyses might help to resolve this key issue?	Updated analyses of OS using the later DCO and incorporation of these analyses into the economic model would help to reduce uncertainty. However, it may not be feasible for the company to conduct these analyses within the timescales available for the appraisal.

Issue 2: Uncertainty surrounding the long-term benefits of ripretinib on OS, including the effects of BID dosing

Report section	4.3.5 critical appraisal points 3 and 5
Description of issue and why the EAG has identified it as important	The company's base case model uses log-logistic models fitted to switching-adjusted OS data in the BSC group and BID-unadjusted OS data in the ripretinib group. The EAG has the following key concerns regarding the company's survival analysis: • The visual fit of the OS models in the ripretinib group is poor. More flexible models such as restricted cubic splines (RCS) may have been better able to reflect the shape of the empirical hazard function for OS. • The company's selected log-logistic model gives a predicted probability of ripretinib OS at 10 years of [REDACTED]. The minutes of the company's 2024 advisory board meeting suggest that overall, the clinical advisors considered that a model-predicted probability of OS of [REDACTED] at 10 years was an overestimate and a probability of [REDACTED] was more realistic. One advisor commented that [REDACTED] OS at 10 years is plausible because treatments are improving and new options are being developed; however, this advisor's view does not relate to expected OS if ripretinib was added to the current treatment pathway for GIST. • Clinical experts consulted by the company agreed that ripretinib 150mg BID dosing would have a "<i>non-negligible</i>" impact on OS. The EAG's clinical advisors stated that they would expect BID dosing to improve OS but that the magnitude of the benefit is uncertain. The company's base case model uses OS data which do not include any adjustment for the effects of BID dosing. The use of BID-unadjusted OS data is likely to overestimate expected survival for ripretinib 150mg QD.
What alternative approach has the EAG suggested?	The EAG's clinical advisors considered that the Weibull and exponential models fitted to the BID-unadjusted OS data provide more plausible predictions of long-term OS for ripretinib (predicted probabilities of 10-year OS = [REDACTED] and [REDACTED], respectively). The EAG's clinical advisors also preferred the generalised gamma model for the BSC group; this model was also applied in the ERG's preferred analysis in TA881. However, the EAG's preferred analysis includes adjustment of the ripretinib OS data to account for the effects of BID dosing using the complex two-stage estimation model based on the generalised gamma distribution, including re-censoring. The EAG's preferred analysis uses the log-logistic model fitted to these adjusted data because it gives a predicted probability of 10-year OS for ripretinib of [REDACTED] which is close to the estimate of [REDACTED] deemed plausible by the clinical experts at the company's advisory board meeting. The 10-year OS probability from this model is similar to, albeit slightly higher than, OS predicted by the exponential and Weibull models fitted to the unadjusted data.
What is the expected effect on the cost-effectiveness estimates?	Including a decision modifier of 1.7, the EAG's corrected version of the company's updated model suggests an ICER of £28,703 per QALY gained (EA1). The inclusion of the generalised gamma model fitted to the switching-adjusted BSC OS data and the exponential model fitted to the BID-unadjusted ripretinib OS data leads to an ICER of £36,321 per QALY gained (EA2). The use of the log-logistic OS model fitted to the BID-adjusted ripretinib OS data (generalised gamma, 2-stage, complex model, with re-censoring) and the generalised gamma model fitted to the switching-adjusted BSC OS data suggests an ICER of £52,822 per QALY gained (EA4 - the EAG's preferred analysis). The probabilistic ICER is higher at £55,470 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	Further clinical input may be useful in determining the plausibility of long-term model-predicted OS for ripretinib 150mg QD.

Issue 3: Inconsistency between the health outcomes and costs associated with BID dosing in the company's model

Report section	4.3.5 critical appraisal point 4
Description of issue and why the EAG has identified it as important	The marketing authorisation for ripretinib refers to a dose of ripretinib 150mg QD. However, as noted in Section 1.4, patients in INVICTUS were allowed to dose-escalate to ripretinib 150mg BID after progression. This higher dose reflects an off-label use of ripretinib. The company's base case economic model uses the BID-unadjusted OS data from the ripretinib arm of INVICTUS and applies only the costs of ripretinib 150mg QD dosing. Taken together, this assumes that the same OS outcomes observed in the ripretinib arm of INVICTUS (including the effects of post-progression 150mg BID dosing in some patients) can be achieved by using less of the drug (i.e., using QD dosing in all patients). Clinical experts consulted by the company and the EAG have indicated that they expect BID dosing to improve OS, although the magnitude of this improvement is uncertain. The EAG's clinical advisors stated that they would want to use BID dosing where clinically appropriate, if permitted. However, there is uncertainty about whether BID dosing will be commissioned for use in the NHS.
What alternative approach has the EAG suggested?	Uncertainty about commissioning routes for ripretinib 150mg BID dosing can only be resolved by obtaining further input from NHS England. Depending on whether ripretinib BID dosing is commissioned, the EAG believes that the following approaches would address the inconsistency between the health outcomes and costs in the company's model: (1) If BID dosing is not commissioned, the model should use the BID-adjusted OS data for ripretinib and exclude the costs of BID dosing. The EAG's preferred analysis (EA4) reflects this situation. (2) If BID dosing is commissioned, the model should use the BID-unadjusted OS data and include the costs of BID dosing, based on the proportion of the post-progression treatment time spent on this higher dose in INVICTUS (60.1%). The EAG's additional sensitivity analysis (ASA) 1 reflects this situation.
What is the expected effect on the cost-effectiveness estimates?	Including a decision modifier of 1.7, the EAG's preferred analysis (assuming QD dosing only) suggests a deterministic ICER of £52,822 per QALY gained (EA4). The probabilistic ICER is higher at £55,470 per QALY gained. The EAG's sensitivity analysis which uses BID-unadjusted OS data and includes the costs of BID dosing for 60.1% of the post-progression treatment time leads to deterministic ICERs ranging from £31,457 to £43,807 per QALY gained, depending on which parametric survival model is selected.
What additional evidence or analyses might help to resolve this key issue?	Further information from NHS England is required to determine whether BID dosing would be commissioned in the NHS and therefore whether the effects and costs of BID dosing should be incorporated into the analysis.

1.6 Summary of EAG's preferred model and sensitivity analysis results

The results of the EAG's preferred model and additional sensitivity analyses are summarised in Table 2. Exploratory analysis 1 (EA1) reflects the EAG-corrected version of the company's model (deterministic). EAs 2-4 also include these corrections. EA4 is the EAG's preferred model.

The company's updated base case model suggests that the deterministic ICER for ripretinib versus BSC is £28,730 per QALY gained. The EAG's preferred model suggests a higher ICER of £52,822 per QALY gained. The main driver for this higher ICER is the adjustment of the ripretinib OS data to account for the effects of ripretinib 150mg BID dosing using the two-stage method. The EAG's additional sensitivity analyses indicate that the ICER for ripretinib is likely to be lower when the OS data are not adjusted for BID dosing and instead the costs of BID dosing are included in the analysis. The EAG's other sensitivity analyses indicate that the ICER for ripretinib is sensitive to: the choice of parametric survival model for OS; whether the BID-adjustment of OS includes re-censoring; whether the BSC OS data are adjusted for treatment switching and the choice of parametric survival model selected for TTD.

Table 2: Summary of EAG's preferred model results (deterministic), ripretinib versus BSC

Analysis	Inc. QALYs	Inc. Costs	ICER (including DM)	DM	Difference in ICER from company's base case or EAG preferred analysis
Company's base case (CS)			£28,836	1.7	-
Company's base case (updated)			£28,730	1.7	-
EA1: Correction of errors			£28,703	1.7	£27
EA2: Selection of alternative OS models (ripertinib = BID-unadjusted exponential; BSC = gen. gamma)			£36,321	1.7	£7,590
EA3: Selection of alternative OS models (ripertinib = BID-adjusted log-logistic; BSC = log-logistic)			£55,113	1.7	£26,383
EA4 - EAG preferred			£52,822	1.7	£24,092
ASA1: Alternative OS models unadjusted for BID dosing, includes BID dosing costs					
ASA1a: Exponential			£42,414	1.7	£10,408
ASA1b: Weibull			£43,807	1.7	£9,015
ASA1c: Gompertz			£31,457	1.7	£21,365
ASA1d: Log-normal			£31,868	1.7	£20,954
ASA1e: Log-logistic			£32,727	1.7	£20,094
ASA1f: Generalised gamma			£33,296	1.7	£19,526
ASA2: Alternative OS models adjusted for BID (with re-censoring), excludes BID dosing costs					
ASA2a: Exponential			£56,572	1.7	£3,750
ASA2b: Weibull			£72,639	1.7	£19,818
ASA2c: Gompertz			£73,815	1.7	£20,993
ASA2d: Log-normal			£48,656	1.7	£4,166
ASA2e: Log-logistic			£52,822	1.7	£0
ASA2f: Generalised gamma			£72,868	1.7	£20,046
ASA3: Alternative OS models adjusted for BID (without re-censoring), excludes BID dosing costs					
ASA3a: Exponential			£45,110	1.7	£7,712
ASA3b: Weibull			£45,589	1.7	£7,232
ASA3c: Gompertz			£21,813	1.7	£31,009

Analysis	Inc. QALYs	Inc. Costs	ICER (including DM)	DM	Difference in ICER from company's base case or EAG preferred analysis
ASA3d: Log-normal			£34,297	1.7	-£18,525
ASA3e: Log-logistic			£34,731	1.7	-£18,091
ASA3f: Generalised gamma			£30,149	1.7	-£22,673
ASA4: Alternative TTD models					
ASA4a: Exponential			£52,822	1.7	£0
ASA4b: Weibull			£52,469	1.7	-£353
ASA4c: Gompertz			£53,018	1.7	£197
ASA4d: Log-normal			£58,858	1.7	£6,037
ASA4e: Log-logistic			£61,355	1.7	£8,533
ASA4f: Generalised gamma			£53,627	1.7	£805
ASA5: Alternative PFS models					
ASA5a: Exponential			£52,493	1.7	-£329
ASA5b: Weibull			£52,473	1.7	-£349
ASA5c: Gompertz			£52,559	1.7	-£263
ASA5d: Log-normal			£52,822	1.7	£0
ASA5e: Log-logistic			£55,031	1.7	£2,209
ASA5f: Generalised gamma			£52,521	1.7	-£301
ASA6: Alternative placebo group switching OS adjustment					
ASA6a: Unadjusted			£219,436	1.2	£166,614
ASA6b: Two stage adjusted simple without re-censoring			£53,944	1.7	£1,122
ASA6c: Two stage adjusted complex without re-censoring			£57,494	1.7	£4,673
ASA6d: Two stage adjusted complex with re-censoring			£55,569	1.7	£2,748
ASA6e: RPSFTM adjusted without re-censoring			£55,551	1.7	£2,729
ASA6f: RPSFTM adjusted with re-censoring			£48,774	1.7	-£4,048
ASA6g: RPSFTM adjusted with common treatment effect relaxed (ki=0.5; Weibull)			£49,763	1.7	-£3,059
ASA6h: RPSFTM adjusted with common treatment effect relaxed (ki=0.5)			£65,442	1.7	£12,620
ASA7: Alternative health state utility values (GRID values)			£52,342	1.7	-£480

ASA - additional sensitivity analysis; BID - twice daily; CS - company's submission; DM - decision modifier; EA - exploratory analysis; EAG - External Assessment Group; gen. gamma - generalised gamma; ICER - incremental cost-effectiveness ratio; Inc. - incremental; OS - overall survival; PFS - progression-free survival; QALY - quality-adjusted life year; RPSFTM - rank-preserving structural failure time model; TTD - time to treatment discontinuation

Modelling errors identified by the EAG are described in Section 4.3.5. For further details of the exploratory and sensitivity analyses undertaken by the EAG, see Section 5.2.1.

2. BACKGROUND

This report evaluates ripretinib for the treatment of adults with advanced gastrointestinal stromal tumours (GISTs) who have received prior treatment with three or more kinase inhibitors, including imatinib. This assessment has been conducted to inform the re-appraisal of NICE Technology Appraisal (TA) 881.¹ As with TA881, the main evidence to inform the clinical effectiveness of ripretinib comes from the INVICTUS randomised controlled trial (RCT).² The main difference between the company's submission (CS) presented in TA881 and the submission for the current appraisal relates to the company's proposed use of ripretinib, which now includes the use of ripretinib prior to and following disease progression for patients who are still deriving benefit from treatment (i.e., the proposed treatment stopping rule in TA881 no longer forms part of the company's value proposition). As the clinical evidence informing the economic model for this appraisal remains unchanged from TA881, some sections of this EAG report are based on the same content contained in the Evidence Review Group (ERG) report which was produced to inform the earlier appraisal. This EAG report also includes reference to clinical input received by the ERG in TA881.

This chapter presents a brief summary and critique of the company's description of the disease, the company's overview of the current treatment pathway and its intended positioning of ripretinib, and a summary and critique of the decision problem addressed in the CS.³

2.1 Company's description of the underlying health problem

2.1.1 Overview of GIST

The company's description of the disease (Section 1.4 of the CS³) is summarised briefly here together with additional information from the previous ERG report for TA881⁴ as well as further input from the EAG's clinical advisors. The EAG's clinical advisors agree that the company's description of GIST is broadly accurate.

Soft tissue sarcomas account for 1% of malignancies in adults, and GISTs account for approximately 7% of all soft tissue sarcomas.⁵ GIST is a mesenchymal tumour of the gastrointestinal (GI) tract. GIST most frequently develops in the stomach (60-70% of cases) or small intestine (25-35% of cases), or in the colon, rectum or other rare sites (4-5% of cases).³ The median age at presentation is between 60 and 65 years. GIST is not commonly diagnosed in people aged under 40 years (<10%).⁶

The majority of patients present with symptoms at diagnosis and approximately half have acute or chronic GI bleeding.⁷⁻⁹ Symptoms of GIST are often non-specific and include GI pain, nausea, early satiety, abdominal bloating, anaemia, detection of an abdominal mass, gastric discomfort or ulcer-like symptoms.^{7, 8, 10-12} Common sites of GIST metastases include the liver (65%) and the peritoneum (21%), whilst less than 10% of tumours metastasise to the lungs or bone.¹³ Disease progression to advanced

stages often has a negative impact on the health-related quality of life (HRQoL) of patients as well as a reduction in cognitive and social functioning. Patients with advanced GIST are often also functionally impaired, with 19% having a baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 or 3.^{14, 15} Section 1.4 of the CS³ states that clinical experts consulted by the company suggested that the expected survival of patients who have received four or more therapies for advanced GIST and who are treated with best supportive care (BSC) is two to three months. The EAG's clinical advisors agreed that the prognosis for these patients is very poor, with few patients receiving BSC alone expected to remain alive after 12 months.

2.1.2 Genetics of GIST

The CS³ (Section 1.1) states that GIST is generally driven by mutations in the KIT (also referred to as CD117) or platelet derived growth factor receptor alpha (PDGFRA) receptor tyrosine kinases. These mutations often lead to constitutively activated KIT or PDGFRA (i.e., their cellular signalling activity is permanently “turned on”). Approximately 80% of GISTs have primary mutations in KIT, and 5-10% have a mutation in PDGFRA. Around 10% of GISTs lack mutations in KIT or PDGFRA genes and are referred to as wild-type; these cases often have mutations in other genes.¹⁶ Most primary KIT mutations involve a single mutation at diagnosis; however, secondary acquired mutations can also occur over time in response to treatment with targeted tyrosine kinase inhibitor (TKI) therapies, leading to treatment resistance. Primary and secondary mutations are a known issue in GIST, and patients may have multiple mutations.

2.2 Company's overview of current service provision

2.2.1 Primary localised GIST: surgery and adjuvant imatinib

Surgery is the recommended approach for primary and localised GIST and is the only potentially curative option. Around one-third of patients have an intermediate to high risk of disease progression and approximately 50% have disease recurrence within 2 to 3 years following resection.^{8, 17} Patients who are at high risk of recurrence can receive adjuvant imatinib for up to 3 years.

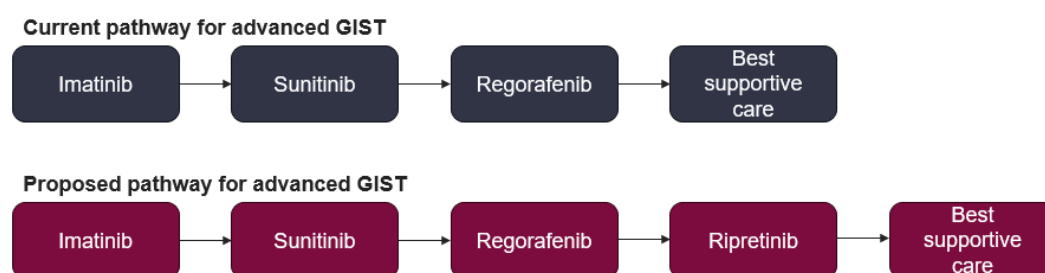
2.2.2 Current treatment pathway and proposed positioning of ripretinib

The company's view of the current treatment pathway for advanced GIST and its proposed positioning of ripretinib is shown in Figure 1. Whilst not shown in the diagram, each TKI would be given alongside BSC. The CS³ (Section 1.4.2) states that approximately 50% of patients present with metastatic or unresectable GIST at diagnosis and around 40-90% of surgical patients develop subsequent recurrence or metastasis.^{18, 19} Targeted therapy with TKIs is the standard of care for metastatic or unresectable GIST due to their anti-KIT and anti-PDGFRα properties. Imatinib is the standard first-line treatment in England. Disease progression after imatinib treatment occurs mostly due to primary resistance, secondary KIT mutation or inadequate drug exposure. If progression or imatinib intolerance is

confirmed, the standard second-line treatment is sunitinib. Most patients will experience relapse again within 6 months to 1 year due to additional or alternative secondary mutations in KIT, or due to multiple different KIT mutations occurring in different areas of the tumour. In addition, some imatinib-resistant patients have primary resistance to sunitinib due to the specific secondary mutation(s) that arise during imatinib treatment. Regorafenib is regarded as standard therapy for the third-line treatment of patients who progress on or fail to respond to imatinib and sunitinib.

The CS³ (Section 1.4.2) states that there is no established standard care for GIST patients in the UK who have received prior treatment with three or more TKIs, including imatinib, other than BSC. The CS highlights that some patients may be enrolled into clinical trials or, as a last resort, they may be offered continued post-progression regorafenib. The company's proposed positioning in the treatment pathway for advanced GIST is shown in Figure 1. The CS describes the proposed positioning of ripretinib as a 4L therapy; however, at the factual accuracy check (FAC) stage of the appraisal, the company clarified that the proposed positioning of ripretinib is as a fourth- and subsequent-line (4L+) therapy. Whilst not explicitly shown in Figure 1, the company is seeking a positive recommendation from the National Institute for Health and Care Excellence (NICE) for ripretinib treatment prior to and following disease progression (for patients who are still obtaining benefit from treatment).

Figure 1: Current treatment pathway for advanced GIST (reproduced from CS, Figure 1)



GIST - gastrointestinal stromal tumour

2.2.3 EAG's critique of the company's treatment pathway and positioning of ripretinib

The EAG's clinical advisors agreed that the company's description of the current treatment pathway is accurate. The company's proposed positioning of ripretinib within the pathway is consistent with the final NICE scope²⁰ and the marketing authorisation for ripretinib.²¹

In TA881,¹ the EAG's clinical advisors commented that a large proportion of patients (50% or more) who progress on third-line regorafenib will continue to receive this treatment after disease progression if they are still tolerating and deriving clinical benefit from it and there are no other alternative treatment options, whilst the remainder will receive BSC alone. The relevance of regorafenib as a comparator for ripretinib is discussed briefly in Section 2.3.3. One of the EAG's clinical advisors stated that in the

absence of other therapies beyond third-line, they may sometimes consider rechallenging using imatinib, but that this approach does not reflect standard of care.

The EAG's clinical advisors agreed with the company's proposed use of ripretinib beyond disease progression and commented that the continued use of TKI therapy in patients with active disease progression is consistent with clinical recommendations on the use of TKIs in patients with advanced and progressed GIST published by the National Comprehensive Cancer Network [NCCN] Task Force²² and UK clinical practice guidelines for the management of GIST.²³ The 2022 update to the NCCN guidelines²⁴ does not mention the use of continued regorafenib following progression on third-line therapy as it instead recommends ripretinib as 4L therapy. The 2024 update to the British Sarcoma Group guideline mentions that post-progression regorafenib is sometimes used, but places greater emphasis on the need to recruit patients into clinical trials, when available.²⁵

2.3 Critique of company's definition of the decision problem

A summary of the decision problem as outlined in the final NICE scope²⁰ and addressed in the CS³ is presented in Table 3. The EAG's critique of the decision problem addressed within the CS is presented in the subsequent sections.

Table 3: The decision problem (reproduced from CS, Table 1)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with advanced GIST who have received prior treatment with three or more kinase inhibitors, including imatinib	As per scope	N/a
Intervention	Ripretinib	As per scope	N/a
Comparator(s)	Established clinical management.	Best supportive care (BSC)	The specific comparator should be BSC, where BSC is established clinical management of 4 th line ($\geq 4L$) advanced GIST.
Outcomes	The outcome measures to be considered include: • Overall survival • Progression free survival • Response rate (including partial response rate and duration of response) • Stable disease • Adverse effects of treatment • Health-related quality of life.	As per scope	N/a
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.	As per scope	N/a

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • People whose disease progressed after previous treatment with tyrosine kinase inhibitors • People whose disease is resistant or intolerant to tyrosine kinase inhibitors	Subgroups not considered	There is no differentiation in clinical guidelines or clinical practice based on subgroups for the 3 prior lines of therapy in advanced GIST; as such the INVICTUS trial protocol did not make this distinction
Special considerations including issues related to equity or equality	None identified.	There are no special considerations relating to issues of equity or equality.	N/a

NICE - National Institute for Health and Care Excellence; GIST - gastrointestinal stromal tumour; BSC - best supportive care; N/a - not applicable

2.3.1 Population

The final NICE scope²⁰ specifies the relevant population as adults with advanced GIST who have received prior treatment with three or more TKIs, including imatinib. The main clinical evidence for ripretinib included in the CS³ comes from the INVICTUS RCT.² Patients enrolled in INVICTUS were adults with advanced GIST with progression on at least imatinib, sunitinib, and regorafenib or documented intolerance to any of these treatments despite dose modifications. The European Medicines Agency (EMA) and Medicines and Healthcare products Regulatory Agency (MHRA) marketing authorisation for ripretinib relates to “*adult patients with advanced gastrointestinal stromal tumour (GIST) who have received prior treatment with three or more kinase inhibitors, including imatinib.*”²¹ As such, the populations defined in the NICE scope, the key clinical evidence and the marketing authorisation for ripretinib are all broadly aligned.

2.3.2 Intervention

The intervention described in the CS³ is consistent with the final NICE scope.²⁰ The intervention under consideration is ripretinib (Qinlock®). Ripretinib is a novel TKI which inhibits KIT proto-oncogene receptor tyrosine kinase and PDGFRA kinase, including wild-type, primary, and secondary mutations. Ripretinib also inhibits other kinases *in vitro*, such as PDGFRB, TIE2, VEGFR2, and BRAF.²¹

A full marketing authorisation for ripretinib was issued by the MHRA in December 2021. According to the Summary of Product Characteristics (SmPC) for ripretinib,²¹ the recommended dose is 150mg ripretinib (three 50mg tablets) taken once daily (QD) at the same time each day with or without food. Ripretinib is administered orally in tablet form. The list price per pack of 90 x 50mg ripretinib tablets (30 days' supply) is £18,400.²⁶ The CS³ states that a Patient Access Scheme (PAS) has been proposed for ripretinib: this takes the form of a simple price discount of [REDACTED]. The price per pack of ripretinib including the PAS is [REDACTED].

The INVICTUS trial² allowed patients in the ripretinib group to continue to receive the study drug after disease progression. The SmPC for ripretinib²¹ states that treatment with ripretinib should continue as long as benefit is observed or until unacceptable toxicity; as such, treatment beyond disease progression is permitted within the marketing authorisation. The EAG's clinical advisors commented that if ripretinib was recommended by NICE, they would want to be able to continue to offer treatment with ripretinib beyond disease progression if patients were still deriving clinical benefit from it. The clinical experts consulted by the EAG and the company commented that they expected continued ripretinib given after disease progression to improve OS.²⁷ In contrast to the company's earlier submission in TA881,¹ the proposed use of ripretinib within the CS for the current appraisal includes the use of post-progression ripretinib.

The INVICTUS trial² also permitted the use of intra-patient dose escalation (IPDE) to ripretinib 150mg BID (twice daily) following disease progression on ripretinib 150mg QD in both treatment groups. Clinical experts consulted by the company commented that the 150mg BID dosing regimen is expected to have led to a “*non-negligible*” impact on OS. The EAG’s clinical advisors stated that they would expect BID dosing to improve OS but that the magnitude of the benefit is uncertain. The 150mg BID dosing regimen is not mentioned in the ripretinib SmPC,²¹ except in the situation whereby ripretinib is co-administered alongside strong or moderate CYP3A inducers, and therefore represents an off-label use of the drug. The EAG’s clinical advisors stated that they would want to be able to use 150mg BID dosing post-progression, if permitted and where clinically appropriate. The company’s proposed use of ripretinib in the CS³ is limited to the use of the 150mg QD (once daily) dose. The company’s base case economic model applies the outcomes observed in INVICTUS² (including IPDE to the ripretinib 150mg BID dose in some patients) with ripretinib costs restricted to the 150mg QD dose (see Section 4.3.5).

The CS³ states that additional testing is required for people prior to and during treatment with ripretinib. This includes: (i) monitoring for people with a history of high blood pressure which may require blood pressure medication, as clinically indicated; (ii) ejection fraction assessment using an echocardiogram or multiple gated acquisition (MUGA) scan prior to initiating and during treatment with ripretinib, as clinically indicated, and (iii) dermatological evaluations due to the increased risk of squamous cell carcinoma (SCC).

2.3.3 Comparators

The final NICE scope²⁰ includes a single comparator - established clinical management. The INVICTUS trial² was placebo-controlled (given alongside BSC), and the comparator considered in the CS³ and the company’s economic model is BSC alone. Patients who were randomised to the placebo group of INVICTUS were permitted to switch treatment to receive ripretinib after disease progression; the company’s economic model includes statistical adjustment of the OS data to account for potential confounding caused by treatment switching onto ripretinib in the placebo arm of the trial; these methods are described in Section 4.2.4.

In TA881,¹ the ERG’s clinical advisors commented that a large proportion of patients who have progressed on third-line regorafenib (after previously failing earlier treatment with both sunitinib and imatinib) continue to receive regorafenib if they are still obtaining benefit from it. The clinical advisors also stated that if ripretinib received a positive NICE recommendation, they would switch patients onto 4L ripretinib as soon as they progress on third-line regorafenib. On this basis, continued post-progression regorafenib may be considered as a relevant comparator to ripretinib. However, in TA881, the company was unable to identify sufficient evidence to inform a reliable indirect treatment comparison (ITC) between ripretinib and regorafenib. The Appraisal Committee acknowledged that the

absence of such a comparison introduced uncertainty, but concluded that BSC is likely the most appropriate comparator for the appraisal, given the available evidence.¹ The EAG believes that evidence on PFS and OS outcomes for continued post-progression regorafenib is still lacking and therefore this issue is not discussed in detail in this EAG report.

2.3.4 Outcomes

The following outcomes are listed in the final NICE scope:²⁰

- Progression-free survival (PFS)
- Overall survival (OS)
- Response rate (including partial response rate and duration of response)
- Stable disease
- Adverse effects of treatment
- Health-related quality of life (HRQoL).

The CS³ reports on all of these outcomes for the ITT population of INVICTUS.² The company's economic model is informed by data on PFS, time to treatment discontinuation (TTD), OS, adverse events (AEs) and HRQoL from INVICTUS (see Section 3.2.4).

2.3.5 Other relevant factors

Section 1.5 of the CS³ states that there are no known equality issues relating to the use of ripretinib for treating advanced GIST after three or more therapies.

3. CLINICAL EFFECTIVENESS

The clinical evidence contained in the CS³ is comprised of:

- A systematic literature review (SLR)
- Summary and results of the INVICTUS² trial of ripretinib.
- Summary and results of real-world evidence (RWE) from the Royal Marsden expanded access cohort study.²⁸

This chapter summarises and critiques the company's review methods and the clinical effectiveness data contained in the CS.³ Full details are presented in Section 2 of the CS and CS Appendices B, C, and D.²⁹

3.1 Critique of the methods of review

3.1.1 Searches

The company performed an SLR to identify all clinical effectiveness and safety studies of ripretinib or comparator treatments for advanced, unresectable, or metastatic patients with 4L+ GIST. The company performed an initial SLR in July 2020 followed by five updates in July 2021, March 2022, May 2023, April 2024 and March 2025 (CS, Appendix D).²⁹

The EAG identified two main limitations in the clinical effectiveness searches:

- Restricted terms and fields to search for prior treatments (4L+ studies)
- The absence of intervention and comparator terms from the searches.

The company searched a single Ovid host platform that comprises a suite of databases including: MEDLINE; Embase; Cochrane Database of Systematic Reviews (CDSR); Cochrane Central Register of Controlled Trials (CENTRAL); ACP Journal Club; Database of Abstracts of Reviews of Effects (DARE); Cochrane Clinical Answers; Cochrane Methodology Register; Health Technology Assessment (HTA); NHS Economic Evaluation Database (NHS EED) and EconLit. The company hand searched the bibliographies of relevant SLRs to identify other new studies for inclusion.

Three conference abstract websites were also searched for the last five years (2021-2025): American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO) and ASCO Gastrointestinal Cancers Symposium. The company searched clinicaltrials.gov for ongoing, completed or unpublished trials. Four HTA agency websites were also searched: NICE; Scottish Medicines Consortium (SMC); Pharmaceutical Benefits Advisory Committee (PBAC); and Canada's Drug Agency (CDA-AMC).

The company applied multiple concept combinations to the search for the population (disease GIST AND “metastatic/advanced/unresectable” AND relapsed/refractory/resistant). The company’s searches also applied a limit to patients who have had prior treatment by searching for the drugs imatinib, sunitinib and regorafenib (see CS Appendix B,²⁹ statement 19 in Table 4: Search strategy: Clinical SLR). The EAG would have recommended either the inclusion of the synonyms/drug trade names in statement 19 of the electronic search strategy (Table 4 of CS Appendix B²⁹) such as those listed on page 34 of CS Appendix B, i.e., “*gleevec OR glivec OR sti571 OR stivarga OR bay 73-4506 OR sutent OR su011248*”, or the use of “multi-purpose” field as opposed to title and abstract searching (which will search for drug trade names, registry number and chemical name of the drugs). Omitting drug name synonyms results in a lower search recall (i.e., finds fewer relevant studies) which will impact the comprehensiveness of the search. In addition, according to Chapter 4 of the Technical Supplement of the Cochrane Handbook for Systematic Reviews of Interventions,³⁰ .mp field searching is preferred over title and abstract field searching for interventions as it increases the sensitivity of the search because the relevant terms could be found elsewhere such as the subject headings.

The company restricted the database searches to English language publications. According to the Cochrane Handbook,³⁰ applying language filters to restrict the search may lead to publication language bias, where relevant studies published in other languages are excluded.

The EAG suggests that the drug term ripretinib should have been included in the ‘prior therapy’ concept search statement, as there will invariably be studies where the prior therapies are not mentioned in the title and abstracts. The EAG repeated the company’s MEDLINE and Embase search which showed that only 26 out of 39 included studies would be retrieved in the RCT search. However, if the term ripretinib was included in the strategy, this would find a further four of the included studies: Becker *et al.*, 2021;³¹ Zalberg *et al.*, 2021;³² von Mehren *et al.*, 2019;³³ and Janku *et al.*, 2020.³⁴

The EAG also recommends the inclusion of the comparator terms listed in the SLR eligibility criteria, and the ‘approved interventions’ and ‘other interventions’ listed in the included studies (Tables 5 and Table 6 of CS Appendix B²⁹).

Given the limitations mentioned above, the EAG believes that the company’s electronic search strategy alone is not sufficient to find all relevant studies. The company’s supplementary searches, which include reference tracking and grey literature searches, may have mitigated the impact of the limitations described above.

3.1.2 Inclusion criteria for the SLR

The clinical SLR described in the CS³ is broader than the decision problem defined in the NICE scope.²⁰ The SLR included RCTs and single-arm interventional studies of patients with advanced GIST

receiving 4L+ therapy, published from the year 2000 onwards. The included interventions were: ripretinib; imatinib; regorafenib; sunitinib; BSC and other interventions for 4L+ GIST. The EAG considers the inclusion criteria to be appropriate to identify RCTs of ripretinib for the 4L+ treatment of GIST.

3.1.3 Critique of study selection, data extraction and quality assessment

The CS³ does not report details about the process used for study selection, data extraction or quality assessment. Following a request for clarification from the EAG³⁵ (question A1), the company confirmed that screening, data extraction and quality assessment were undertaken by two independent reviewers, and checked by a third independent analyst. The EAG considers these methods to be appropriate. The company assessed the quality of the included INVICTUS RCT² using the NICE quality assessment checklist (CS Appendix B1.3).²⁹ However, the CS did not include a quality assessment of the Royal Marsden expanded access cohort study.²⁸ Following a request from the EAG³⁵ (question A8) the company quality assessed this study using the Critical Appraisal Skills Programme (CASP) Cohort Study Checklist. The EAG considers the use of these quality assessment tools to be appropriate.

3.1.4 EAG's view on the company's review methods

Overall, the EAG considers that the majority of the company's review methods were appropriate, with the exception of the limitations in the search methods described in Section 3.1.1.

3.1.5 Results of the company's SLR

The company's clinical SLR identified 39 publications, 15 of which assessed ripretinib and were relevant to this submission (see CS,³ Section 2.2, Table 3). Of these, 10 publications related to the INVICTUS trial of ripretinib, the primary references being the INVICTUS Clinical Study Report (CSR)² and Blay *et al.* (2020).³⁶ Two publications^{37, 38} were related to a Phase 2 single-arm, open-label study of ripretinib (NCT04282980) and a further two publications^{34, 39} related to a Phase 1 non-randomised dose escalation study of ripretinib (NCT02571036). These publications are not discussed further in the CS³ or in this EAG report. Therefore, the SLR identified only one relevant study: the INVICTUS RCT of ripretinib.² Although outside the remit of the SLR for the clinical effectiveness, the CS presents details of the methods and results of an RWE study undertaken at the Royal Marsden Hospital in London (UK) as part of an expanded access programme.²⁸ The CS³ notes that this study was not used to inform the company's economic model due to its retrospective nature, shorter follow-up period and smaller sample size compared with INVICTUS.² In addition, the CS³ also included insights from three advisory board meetings with oncologists based in the UK; these meetings were held in August 2022, July 2024 and April 2025.^{27, 40, 41}

3.2 Characteristics of INVICTUS study of ripretinib

3.2.1 Study design: INVICTUS

The company's SLR identified one relevant RCT of ripretinib.² INVICTUS is an international, multicentre, randomised, double-blind, placebo-controlled Phase 3 trial in patients with advanced GIST after at least three prior anticancer therapies. INVICTUS compared the efficacy of ripretinib plus BSC versus placebo plus BSC (CS,³ Section 2.3). The study was conducted at 29 specialised hospitals across 12 countries across North America, Europe, and Asia. The design of the INVICTUS RCT is summarised in Table 4 and Figure 2.

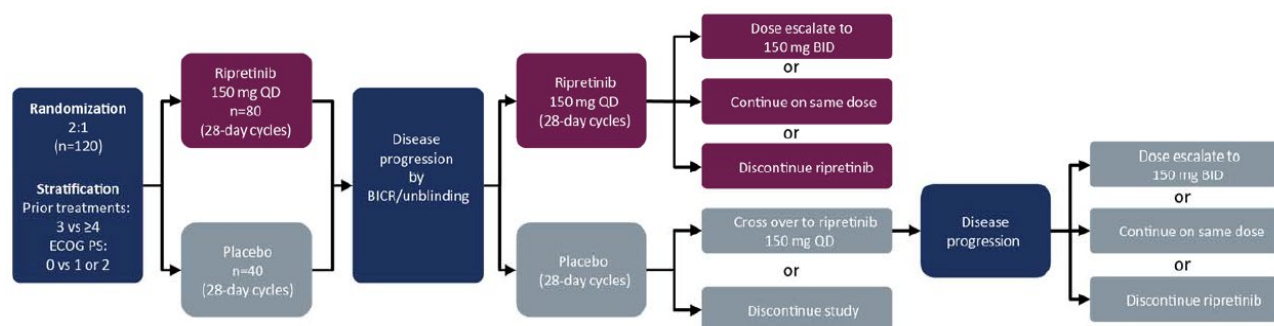
Table 4: Design of the INVICTUS study (adapted from CS, Tables 4, 6 and 7)

Study	INVICTUS (NCT03353753)
Study design	Phase 3, multicentre, double-blind, placebo-controlled, randomised trial
Settings and locations	29 specialised hospitals in North America, Europe, and Asia (2 in the UK)
Population	• Patients with GIST aged ≥ 18 years • ECOG PS of 0-2 at screening • Disease progression on (at least) imatinib, sunitinib and regorafenib, or documented intolerance to any of these (i.e., fourth-line or later) • At least 1 measurable lesion according to the mRECIST v1.1 criteria within 21 days of the first dose of study drug • Adequate organ function and bone marrow reserve • Resolution of all toxicities from prior therapy to $\leq$ Grade 1 (or baseline) within 1 week prior to the first dose of study drug
Key Exclusion	• Treatment with anticancer therapy, including investigational therapy or investigational procedures, within 14 days or 5x the half-life (whichever was longer) prior to the first dose of study drug. For prior biological therapies, e.g., monoclonal antibodies with a half-life longer than 3 days, the interval was at least 28 days prior to the first dose of study drug. • Prior treatment with ripretinib
Randomisation stratification factors	• 3 versus ≥ 4 prior anticancer treatments • ECOG PS of 0 versus 1 or 2
Intervention(s)	Ripretinib 150mg QD + BSC (n=85)
Comparator(s)	Placebo + BSC (n=44)
Duration of treatment and options after disease progression	• Ripretinib: 150mg QD until disease progression or unacceptable toxicity. Upon progression, patients randomised to ripretinib could discontinue ripretinib, continue their current dose of 150mg per day, or double their dose to 150mg BID • Placebo: Upon progression, patients randomised to placebo could discontinue the study or cross over to ripretinib 150mg QD
Reported outcomes specified in the decision problem	• PFS • OS • Response rates (including partial response rate and duration of response) • AEs • HRQoL: EQ-5D-5L, EQ-VAS, EORTC QLQ-C30 (physical and role functioning domains only)

Study	INVICTUS (NCT03353753)
All other reported outcomes	• TTP • Time to best response • TTD
Pre planned subgroups	• Age (18 to 64 vs 65 to 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 PS (0 vs 1 or 2) • Number of prior therapies (3 vs ≥ 4)

AE - adverse event; *QD* - once daily; *BID* - twice daily; *BSC* - best supportive care; *ECOG* - Eastern Cooperative Oncology Group; *mRECIST* - modified Response Evaluation Criteria In Solid Tumors; *EORTC QLQ-C30* - European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-item; *EQ-5D-5L* - EuroQol 5 dimensions (5-level); *EQ-VAS* - EuroQol visual analogue scale; *GIST* - gastrointestinal stromal tumour; *HRQoL* - health-related quality of life; *OS* - overall survival; *PFS* - progression-free survival; *PS* - performance status; *TTP* - time to progression; *TTD* - time to treatment discontinuation

Figure 2: INVICTUS study design and treatment allocation (reproduced from CS, Figure 2)



BID - twice daily; *BICR* - blinded independent central review; *ECOG* - Eastern Cooperative Oncology Group; *PS* - performance status; *QD* - once daily

Note: Randomisation was stratified based on prior lines of therapy (3 vs ≥ 4) and ECOG (0 vs 1 or 2)

Source: Blay et al. 2020,³⁶ supplementary appendix, Figure S1.

Population in INVICTUS

The INVICTUS trial² included 129 patients with advanced GIST who had received at least three prior anticancer therapies including (at least) imatinib, sunitinib and regorafenib. The inclusion criteria for INVICTUS are slightly more restrictive than the final NICE scope²⁰ and the SmPC for ripretinib,²¹ both of which specify the population as patients who have received at least three prior kinase inhibitors, including imatinib. Approximately 37% of patients in INVICTUS had received more than three prior therapies at enrolment (i.e., they were at fifth-line or later).

Intervention in INVICTUS

Patients were randomised 2:1 to ripretinib plus BSC versus placebo plus BSC. In total, 85 patients were randomised to ripretinib and 44 to placebo. The ripretinib dose was 150mg QD (once a day) until disease progression or unacceptable toxicity.

Upon progression, patients and investigators were unblinded, and patients randomised to ripretinib could either discontinue ripretinib, continue their current dose of ripretinib 150mg QD, or double their dose to 150mg BID (twice per day). Patients randomised to placebo could discontinue the study or cross over to receive ripretinib 150mg QD. Patients who crossed over to ripretinib and then experienced a second disease progression were given the option to continue treatment at an increased dose of 150mg BID, to continue their current dose of 150mg QD, or to discontinue treatment with ripretinib. Ripretinib dose interruption or dose reduction was permitted at the discretion of the investigators at any time due to adverse events (AEs). The company's clarification response in TA881⁴² (question A4) states that the rationale for permitting patients in the ripretinib group to double their dose was because this higher dose was well-tolerated in the Phase 1 study (NCT02571036)^{34, 39} and so BID dosing was offered to patients with disease progression in INVICTUS² due to the lack of alternative treatments, even though 150mg QD was established as the recommended dose based on safety, pharmacokinetics, and pharmacodynamics data. The EAG notes that the recommended dose in the SmPC for ripretinib²¹ is 150mg QD, and the company's base case economic model applies the outcomes for the ITT population (including post-progression BID dosing in some patients) and only the costs of QD dose (see Section 4.2).

Comparator in INVICTUS

The comparator in INVICTUS² was placebo plus BSC. The EAG's clinical advisors consider that it was reasonable to compare against placebo plus BSC because there are no further recommended 4L+ therapies in England.

Outcomes in INVICTUS

Outcomes included: PFS; PFS1 (time from randomisation until progressed disease [PD] in patients who received IPDE in the ripretinib arm); PFS2 (time from the first dose of ripretinib 150mg BID to PD or death in patients who received IPDE in the ripretinib arm); OS; time to progression (TTP); response rates; TTD; AEs and HRQoL measured using the 5-level Euroqol 5 dimensions (EQ-5D-5L) questionnaire, the Euroqol visual analogue scale (EQ-VAS) and the physical and role functioning domains of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-item questionnaire (EORTC QLQ-C30).

Study quality of INVICTUS

Quality assessment of INVICTUS² is presented in CS Appendix B1.3.²⁹ The CS³ reports that the study is of high methodological quality in terms of: randomisation; baseline comparability of groups; blinding of patients and staff; no unexpected imbalances in drop-outs; no selective outcome reporting and use of ITT analysis. The EAG largely agrees with the company's quality assessment. However, the EAG notes the following points regarding study design:

- a) There were some differences in baseline characteristics between the groups (see Section 3.2.3)
- b) The study was unblinded on progression, and patients were permitted to continue or change treatment (including dose-escalating to ripretinib 150mg BID) on progression. These factors may have impacted on OS, which was measured until the patient died.
- c) No attempt has been made in the CS³ to integrate the assessment of study quality into the findings reported.

Analysis populations and data cut-offs in INVICTUS

The data cut-offs (DCOs) for INVICTUS² were as follows (CS,³ Section 2.3):

- Primary data cut-off: 31st May 2019 (Blay *et al.*, 2020)³⁶
- Additional analysis with extra 9 months of follow-up: DCO 9th March 2020 (Zalcberg *et al.*, 2020 abstract)⁴³
- Additional analysis with extra 14 months of follow-up: DCO 10th August 2020 (Zalcberg *et al.*, 2021)³²
- Additional analysis with extra 19 months of follow-up: DCO 15th January 2021 (von Mehren *et al.*, 2021 abstract).⁴⁴

In addition, the company's response to clarification question B1³⁵ states that a further DCO of May 2022 was available for OS and safety. However, data relating to this later DCO were not included in the CS and have not been used to inform the company's economic model.

The analysis populations were as follows:

- Primary efficacy analyses were based on the ITT population, defined as all randomised patients (n=129). The period analysed was the double-blind period for all outcomes except OS, which followed up patients until they died.
- Safety population, which included all randomised patients who received at least one dose of study drug (n=128).

3.2.2 Participant flow in INVICTUS

Participant flow for the May 2019 DCO is shown in Figure 3 and Table 5. In total, 129 patients were randomised: 85 to ripretinib and 44 to placebo (one placebo patient did not receive treatment). In the placebo group, 29 of 44 patients (66%) crossed over to ripretinib 150mg QD upon progression, whilst 15 of 44 patients (34%) did not cross over (CS,³ Section 2.6.2). Patient withdrawals in the ripretinib and placebo groups were very similar (2.4% vs 2.3%) in the double-blind period (ITT population) and no patient was lost to follow up.

In the ripretinib group, at the May 2019 DCO, 26 of 85 patients (31%) were still on double-blind ripretinib, 17 of 85 patients (20%) had discontinued double-blind treatment, and 42 of 85 patients (49%)

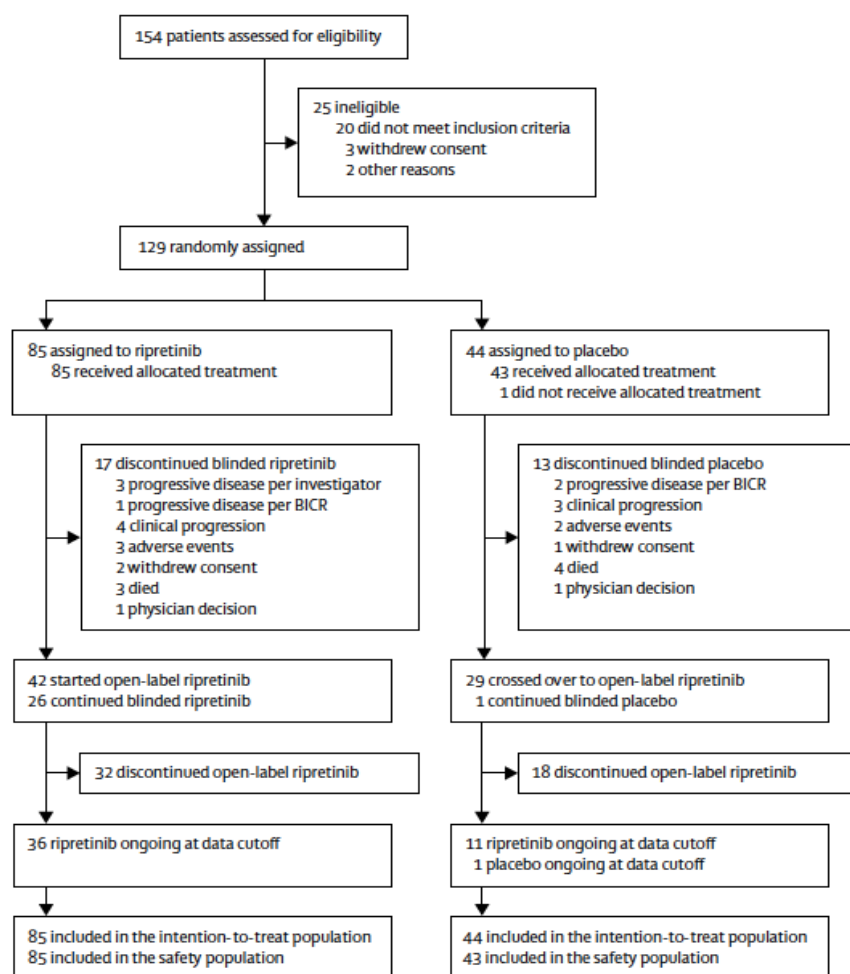
had moved to open-label ripretinib after progression, some of whom later discontinued. One patient remained in the placebo double-blind group and 13 of 44 patients (30.2%) discontinued treatment in the double-blind period. Reasons for withdrawal included clinical progression (ripretinib n=4 [4.7%] vs placebo n=3 [7.0%]) and death (ripretinib n=3 [3.5%] vs placebo n=4 [9.3%]). The proportions of patients still receiving ripretinib (either double-blind or open-label) at the May 2019 DCO were: 36 of 85 patients (42%) in the ripretinib group and 11 of 44 patients (25%) in the placebo group.

Table 5: Participant flow in INVICTUS and proportions still on treatment, May 2019 DCO (reproduced from TA881)

Status	Ripretinib group (N=85)	Placebo group (N=44)
Randomised	85	44
Did not receive treatment	0	1 (2%)
Still on double-blind treatment	26 (31%)	1 (2%)
Discontinued double-blind treatment	17 (20%)	13 (30%)
Moved to open-label ripretinib (150mg QD or 150mg BID)	42 (49%)	29 (66%)
Still receiving open-label ripretinib	10 (12%)	11 (25%)
Discontinued open-label ripretinib	32 (38%)	18 (41%)
Total still receiving ripretinib	36 (42%)	11 (25%)
Total discontinued or not received ripretinib	49 (58%)	33 (75%)

BID - twice daily; QD - once daily; N - number

Figure 3: Flow of participants in the INVICTUS trial, May 2019 DCO (reproduced from CS, Figure 3)

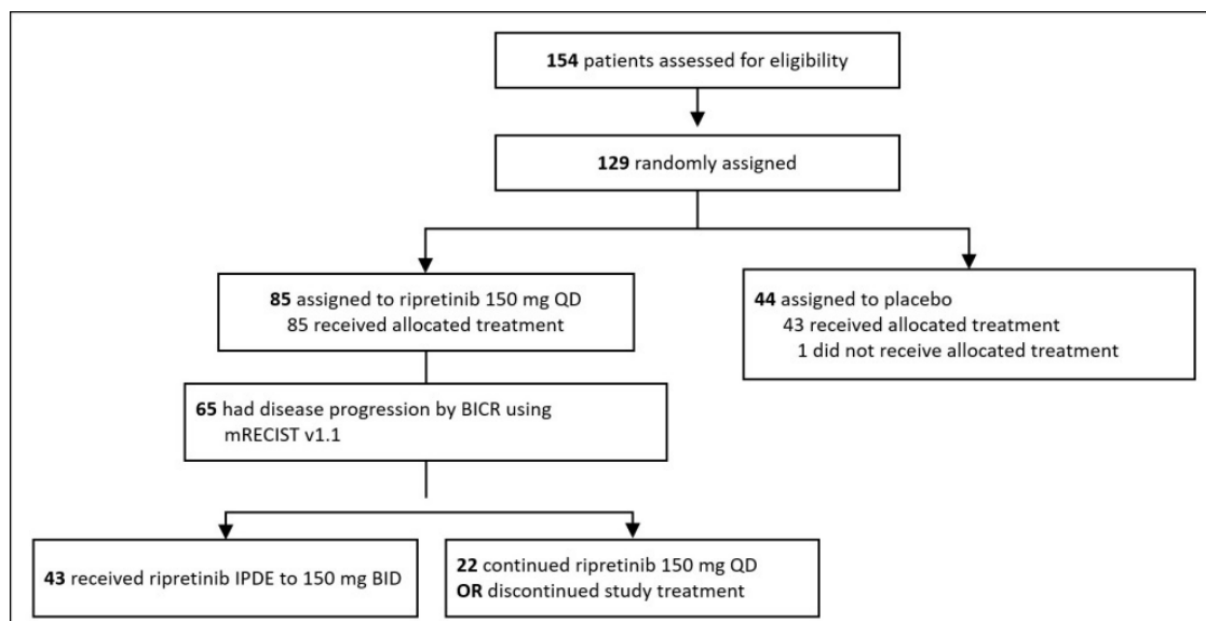


BICR - blinded independent central review

Data reported as of the cut-off date for the primary completion date (31st May 2019)

At the August 2020 DCO, 65 patients in the ripretinib group had progressed, of whom 43 dose-escalated to ripretinib 150mg BID (i.e., IPDE) and 22 did not dose-escalate (see Figure 4). Of these 22 patients, 16 continued ripretinib 150mg QD and 6 discontinued ripretinib (see clarification response,³⁵ question A2). Based on the above information, the EAG infers that 59 patients in the ripretinib group who progressed (i.e., 43 + 16) entered the open-label period, and 6 patients did not. The median duration of treatment with ripretinib 150mg BID was 3.7 months (range: 1 day to 18.6 months) and 11 of 43 patients (26%) received ripretinib 150mg BID for 6 months or longer. Amongst patients who were randomised to the placebo group, 29 of 44 patients (66%) switched to ripretinib after disease progression. Of these, 10 patients continued 150mg QD, 10 had their dose escalated to ripretinib 150mg BID following a second disease progression and 9 discontinued treatment.

Figure 4: Flow of participants in INVICTUS, DCO 10th August 2020 (reproduced from CS, Figure 4)



BICR - Blinded independent central review; BID - twice daily; IPDE - intra-patient dose escalation; mRECIST - modified Response Evaluation Criteria In Solid Tumors; QD - once daily.

Data reported as of 10 August 2020.

Source: Zalcborg et al. 2021³²

As of January 2021, 63 of 85 patients (74%) originally randomised to ripretinib had entered the open-label period following disease progression based on independent radiological review. Of these, 19 patients continued to receive 150mg QD and 44 underwent IPDE to 150mg BID. The company's clarification response³⁵ (question A3) states that 65 patients had progressed at the January 2021 DCO. However, the EAG identified a discrepancy between these figures and those relating to the August 2020 DCO. Specifically, it appears that only 2 patients in the ripretinib group who progressed did not enter the open-label period (65 progressed vs. 63 entered open-label period), which is fewer than the 6 patients previously reported. This discrepancy raises some concerns about the reliability of the company's analyses, particularly those evaluating the impact of post-progression treatment during the open-label period in the ripretinib arm (i.e., the ripretinib arm OS *post hoc* analysis described in Section 3.3.2.1). However, the EAG also notes that the company's response to clarification question A3³⁵ states that the definition of progression used for the aforementioned 65 patients was based on the TTP rule and subsequent treatment received. That is, four patients censored in the TTP analysis but who entered the open-label phase were not included in the 65, while six patients who progressed but did not enter the open-label phase were included. This suggests a total of 69 patients (i.e., 65 + 4) who either progressed and/or entered the open-label phase in the ripretinib arm. If accurate, the difference (69 - 63 = 6 patients) representing those who progressed but did not enter the open-label phase appears reasonable, as this number should technically be equal to or greater than the six patients reported in the August 2020 DCO. Nonetheless, the EAG remains cautious in its interpretation.

At the FAC stage of the appraisal, the company noted the following additional information:

- *2021 DCO (CS description):* 63 patients entered the open-label phase. The company also noted in the FAC form that patients could enter the open-label period prior to BICR-confirmed progression. It should be noted the protocol of the INVICTUS trial specified that *“the open-label portion occur after study treatment unblinding at the time of disease progression based on the independent radiologic review”*.
- *2021 DCO (clarification response, question A3):* 65 patients progressed = 63 patients entered the open-label phase – 4 censored in the PFS analysis but entered the open-label phase + 6 progressed but did not enter the open-label phase.

Given the company’s inconsistent terminology around progression (e.g., whether BICR-confirmed or not) across documents, the EAG remains cautious in interpreting these figures. The acronym TTP was used inconsistently across the CS, the clarification questions, and the protocol. In the INVICTUS protocol, “time-to-progression” and “time-to-tumour progression” seem to be used interchangeably, but it was unclear whether the company’s references to “time-to-progression” sometimes referred instead to the primary PFS analysis (e.g., in reference to clarification question A3 in the company’s FAC form), which was defined slightly differently. These inconsistencies raise concerns about the consistent application of censoring rules across analyses, which the EAG cannot verify.

A final total of 30 of 44 participants (68%) who received placebo in the double-blind period crossed over to receive ripretinib 150mg QD in the open-label period; 16 subsequently dose escalated to 150mg BID following progression with QD dosing.

In response to clarification question A3,³⁵ the company provided data on the duration of post-progression ripretinib treatment for patients randomised to ripretinib who experienced disease progression (see Table 6). The company stated that the data were based on the 65 patients defined as having progressed according to the TTP rules and subsequent treatment received, as described above. Based on the definition provided, the EAG considers that the “QD only group” in Table 6 included the six patients who progressed (BICR-confirmed) but did not enter the open-label phase. Thus, the duration of post-progression ripretinib treatment for patients labelled as “QD only” label should be interpreted with caution, as it contains six patients with post-progression duration of zero, lowering the group mean. The company defined “QD before IPDE” as the time from progression to the start of BID treatment. However, according to the trial design (Figure 2), all patients were expected to switch to BID immediately after progression. The EAG is therefore unclear why any post-progression QD period exists, but considers that this may be due to delays in assessment scheduling. The number of patients in the QD only vs. BID groups in Table 6 also appears to be slightly different from earlier figures reported for this DCO in the CS (19 received post-progression QD; 44 received post-progression BID). At the

FAC stage of the appraisal, the company explained that the values reported in Table 6 were derived from the definition of BICR-confirmed progression used in response to clarification question A3, and were therefore slightly different, as described earlier.

Nevertheless, the EAG considers the mean, minimum, and maximum durations of post-progression ripretinib treatment reported in Table 6 to be reasonable. These data were considered descriptive only and were not used in the company's economic analysis.

Table 6: Duration of post-progression ripretinib treatment in weeks at January 2021 DCO (reproduced from clarification response, question A3)

Ripretinib dose	Number of patients	Mean	SD	Minimum	Maximum
QD only					
QD before IPDE*					
BID					

BID - 150mg twice daily; QD - 150mg once daily; IPDE - intra-patient dose escalation; SD - standard deviation

**Represents the time between progression and patients starting BID treatment*

The CS³ reports that clinicians who attended the UK 2025 advisory board meeting⁴¹ estimated that approximately 80% of all patients receiving ripretinib 150mg QD (as stated in the company's response to clarification question B5³⁵) would be expected to continue ripretinib post-progression in UK clinical practice. Of those on post progression ripretinib, clinicians estimated that around 50% (i.e., 40% of the total population) would dose-escalate if BID dosing was routinely commissioned.⁴¹ At the January 2021 DCO, 63 of 85 (74%) patients had continued ripretinib post-progression, which is comparable to clinical estimates obtained by the company, whilst a higher proportion, 44 of 63 patients (70%), underwent dose escalation in INVICTUS.² The EAG's clinical advisors commented that they would continue to offer treatment with ripretinib beyond disease progression if patients were still deriving clinical benefit from it. They also stated that they would escalate to BID dosing in patients who are fit enough to tolerate it, if permitted. The company's response to clarification question B3³⁵ reflected the clinicians' statement regarding dose escalation in fit patients. Specifically, the company noted that a higher proportion of patients who received an escalated dose of ripretinib after progression had ECOG PS 0 at progression (51.2%) compared to just 16.7% among those who did not escalate.

3.2.3 Baseline characteristics in INVICTUS

Patient baseline characteristics in INVICTUS² are shown in Table 7. The EAG's clinical advisors considered that the characteristics of patients in INVICTUS were generally representative of patients in clinical practice in England and that these were reasonably balanced between groups. The EAG notes that approximately 37% of patients in INVICTUS had received more than three prior therapies. The EAG's clinical advisors noted that patients at later lines of therapy may have a worse prognosis due to pre-treatment and development of resistance mutations; conversely, patients who are still on treatment

at later lines may have a better prognosis due to biologically less aggressive disease. Subgroup analyses of outcomes for INVICTUS are presented in Section 3.3.5 of this EAG report. The EAG requested a breakdown of the number of patients with ECOG PS 1 and ECOG PS 2 (see clarification response,³⁵ question A5). More patients in the trial had ECOG PS 1 than ECOG PS 2 ([REDACTED]).

Patients in the ripretinib group were younger than those in the placebo group (59 vs. 65 years) with fewer patients aged ≥ 75 years (9% vs. 23%). The EAG's clinical advisors noted that this may have had some limited impact on outcomes, favouring ripretinib (see subgroup analyses in Section 3.3.5). The ripretinib group had slightly fewer male patients (55% vs. 59%), slightly more patients with more than three prior therapies (64% vs. 61%) and slightly more patients with ECOG PS 0 (44% vs. 39%). The ripretinib group had a slightly higher frequency of primary gastric tumours (47% vs 41%), a lower frequency of KIT exon 11 mutations (55% vs. 64%) and higher frequency of PDGFRA mutations (4% vs. 0%).

Table 7: Baseline characteristics in INVICTUS (adapted from CS, Table 8 and clarification response, question A5)

Characteristics	Ripretinib (n=85)	Placebo (n=44)
Age		
Median age, range (years)	59 (29–82)	65 (33–83)
18–64	57 (67%)	22 (50%)
65–74	20 (24%)	12 (27%)
≥75	8 (9%)	10 (23%)
Sex		
Male	47 (55%)	26 (59%)
Female	38 (45%)	18 (41%)
Race		
White	64 (75%)	33 (75%)
Non-white	13 (15%)	7 (16%)
Not reported	8 (9%)	4 (9%)
Region		
USA	40 (47%)	20 (46%)
Non-USA	45 (53%)	24 (55%)
Number of previous therapies		
3	54 (64%)	27 (61%)
4–7	31 (36%)	17 (39%)
ECOG PS		
0	37 (44%)	17 (39%)
1 or 2	48 (56%)	27 (61%)
1		
2		
Primary tumour site		
Gastric	40 (47%)	18 (41%)
Jejunum or ileum	20 (24%)	8 (18%)
Mesenteric or omental	6 (7%)	6 (14%)
Other	7 (8%)	4 (9%)
Duodenum	2 (2%)	8 (18%)
Colon or rectum	9 (11%)	0
Unknown	1 (1%)	0
Sum of longest diameters of target lesions (mm), median (range)*	123 (28–495)	142 (17–412)
Primary mutation (central testing of tumour tissue)		
KIT exon 9	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 [†] or not done [‡]	12 (14%)	5 (11%)

ECOG - Eastern Cooperative Oncology Group; PS - performance status; ITT - intention-to-treat; PDGFRA - platelet-derived growth factor receptor α

* Independent assessment. [†] Tumour tissue analysed for baseline mutations but analysis failed. [‡] Biopsy completed per protocol but sample not received for analysis.

Source: Blay et al. 2020,³⁶ Table 1

The EAG notes that despite randomisation in INVICTUS² being stratified by ECOG PS, the placebo group had slightly worse PS and older age. In response to clarification question A6,³⁵ the company stated that, due to the small patient population, stratifying patients by baseline parameters was more

difficult. They also noted that none of the subgroup analyses showed age or ECOG PS to have a statistically significant impact on the benefit of ripretinib (CS,³ Section 2.8.1 and CS Appendix C²⁹). Furthermore, the company reported that similar subgroup analyses considering TKI use at earlier treatment lines for advanced GIST generally showed that age and ECOG PS were not statistically significant treatment effect modifiers (see Table 8).

Table 8: Comparison of subgroup analysis considering different lines of TKI treatment for advanced GIST (reproduced from clarification question, question A6)

	ECOG		Age	
	Overall survival	Progression-free survival	Overall survival	Progression-free survival
Ripretinib (INVICTUS)		Numerically superior HR for ECOG 1 or 2 vs ECOG 0 (95% CIs overlapping)		Numerically superior HR for older age (95% CIs overlapping)
Regorafenib (TA488)⁴⁵	Redacted	Numerically superior HR for ECOG 0 vs ECOG 1 (95% CIs overlapping)	Redacted	Numerically superior HR for older age (95% CIs overlapping)
Sunitinib (TA179)⁴⁶	Suggests ECOG 0-1 favours longer survival vs ECOG 2	Numerically superior HR for ECOG 0 vs ECOG 1 (95% CIs overlapping)	Suggests age <59 years favours longer survival vs age ≥59 years	Numerically superior HR for older age (95% CIs overlapping)

CI - confidence interval; ECOG - Eastern Cooperative Oncology Group; GIST - gastrointestinal stromal tumour; HR - hazard ratio; TKI - tyrosine kinase inhibitor; TA - Technology Appraisal

During the clarification round in TA881⁴² (question A8), the EAG requested data on the percentage of patients who had progressed on, were resistant to, or were intolerant to prior TKIs. However, the company stated that these data were not available. The EAG's clinical advisors noted that patients who were resistant to or progressed on prior therapies may have a worse prognosis than those who switched treatment due to intolerance, and that patients with primary resistance may have a worse prognosis than those progressing later.

3.3 Effectiveness of ripretinib - INVICTUS

Effectiveness data for ripretinib based on the INVICTUS trial² are summarised in this section. Full details are provided in Section 2.6 of the CS³ and CS Appendix C.²⁹ The statistical methods used for the analysis of INVICTUS are reported in CS,³ Section 2.4. Primary efficacy analyses were based on the ITT population, defined as all randomised patients (n=129). The safety population was used for safety analyses and included all patients who received at least one dose of study drug (n=128).

3.3.1 Progression-free survival (PFS)

At the May 2019 DCO, the median follow-up time in the double-blind period was 6.3 months (interquartile range [IQR] 3.2 to 8.2 months) for the ripretinib group and 1.6 months (IQR 1.1 to 2.7 months) for the placebo group.³⁶ As shown in Table 9 and Figure 5, median PFS was 6.3 months for ripretinib versus 1.0 months for placebo. PFS was statistically significantly longer in the ripretinib group than the placebo group (hazard ratio [HR] 0.15, 95% confidence interval [CI] 0.09 to 0.25, $p < 0.0001$). Disease progression or death occurred in 60% of patients in the ripretinib group (34 patients [40%] were censored) and in 84% in the placebo group (7 patients [16%] were censored).³⁶ PFS was very similar at the March 2020 and January 2021 DCOs (Table 9).

PFS2 for patients crossing over from placebo to ripretinib

PFS2 refers to the time from ripretinib initiation after crossover to second disease progression or death (CS,³ Section 2.6). In an exploratory analysis of PFS2 in the open-label period for the 29 (of 44) patients crossing over from placebo to ripretinib 150mg QD at their first disease progression (Table 9 and CS,³ Figure 6), median PFS2 was 4.6 months. Of these 29 patients, 45% (n=13) had a PFS event and 55% (n=16) were censored.

PFS for patients dose escalating on progression - PFS after IPDE to ripretinib 150mg BID

At the 10th August 2020 DCO, amongst 43 (of 85) patients originally randomised to the ripretinib group who dose-escalated to ripretinib 150mg BID upon progression, median PFS1 (time from randomisation to progression in patients who received IPDE in the ripretinib arm) was 4.6 months, and median PFS2 (time from first dose at 150mg BID to progression or death in patients who received IPDE in the ripretinib arm) was 3.7 months (Table 9). The median PFS2/PFS1 ratio was 80% (CS,³ Section 2.6 and CS³ Figure 7).

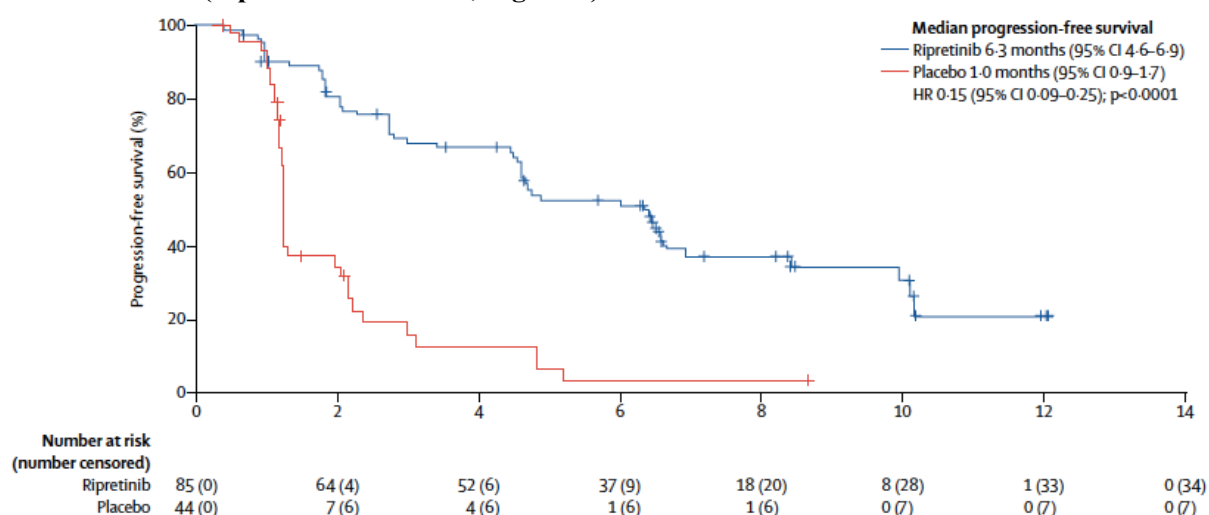
The CS³ states that the clinical experts who attended the advisory board meetings in 2024 and 2025⁴⁰,⁴¹ confirmed that the proportion of patients who remained on treatment with ripretinib beyond progression in INVICTUS² reflects anticipated clinical practice in the UK. The analysis for PFS1 and PFS2 (CS³ Figure 7) only includes patients who dose-escalated to 150mg BID, and the efficacy of continuing ripretinib 150mg QD after progressive disease could not be assessed given the limited number of patients and multiple reasons for continuing ripretinib 150mg QD (not reported during the study) after disease progression. A comparison of PFS for patients who dose escalated to ripretinib 150mg BID versus those continuing 150mg QD was therefore not possible.³²

Table 9: PFS in INVICTUS, as assessed by BICR

Analysis set	DCO	N Ripr	N Pbo	Median PFS, months		HR (95% CI), <i>p</i> -value	Reference in CS
				Ripr	Pbo		
ITT	May 2019	85	44	6.3	1.0	0.15 (0.09 to 0.25), <i>p</i> <0.0001	CS, Section 2.6
	March 2020	85	44	6.3	1.0	0.16 (0.10 to 0.27), <i>p</i> <0.0001	CS, Section 2.6
	January 2021	85	44	6.3	1.0	0.16 (0.10 to 0.27), <i>p</i> <0.0001	CS, Section 2.6
Open-label PFS2 in patients crossing over from placebo to ripretinib	Not reported	-	29	-	4.6	-	CS, Section 2.6
Patients who dose escalated from ripretinib 150mg QD to 150mg BID: PFS1 (time from randomisation to progression or death)	August 2020	43	-	4.6	-	-	CS, Section 2.6
Patients who dose escalated from ripretinib 150mg QD to BID: PFS2 (time from first dose ripretinib 150mg BID to progression or death)	August 2020	43	-	3.7	-	-	CS, Section 2.6

DCO - data cut-off; Ripr - ripretinib; Pbo - placebo; BID - twice daily; BICR - blinded independent central review; CI - confidence interval; HR - hazard ratio; ITT - intention-to-treat; PFS - progression-free survival; QD - once daily; CS - company's submission

Figure 5: Kaplan-Meier plot of PFS assessed by BICR, ITT population, May 2019 DCO (reproduced from CS, Figure 5)



BICR - blinded independent central review; CI - confidence interval; HR - hazard ratio; ITT - intention-to-treat; PFS - progression-free survival

Note: crosses denote censoring of data.

Source: Blay et al. 2020.³⁶

3.3.2 Overall survival (OS)

None of the OS analyses presented in this section include adjustment for treatment switching in the placebo group. The company's methods for adjusting for treatment switching in the placebo group are described separately in Section 4.2.4.

At the May 2019 DCO, 31% of patients in the ripretinib group (69% censored), and 59% in the placebo group (41% censored) had died (see Table 10 and Figure 6). Median OS was 15.1 months for ripretinib versus 6.6 months for placebo. The HR for OS for ripretinib versus placebo was 0.36 (95% CI 0.21 to 0.62, p =not reported [NR]).

As noted in Section 3.2.2, at the May 2019 DCO, 42 of 85 patients (49%) in the ripretinib group and 29 of 44 patients (66%) in the placebo group had received open-label ripretinib after progression. The EAG's clinical advisors stated that continued ripretinib use beyond progression is likely to have extended OS.

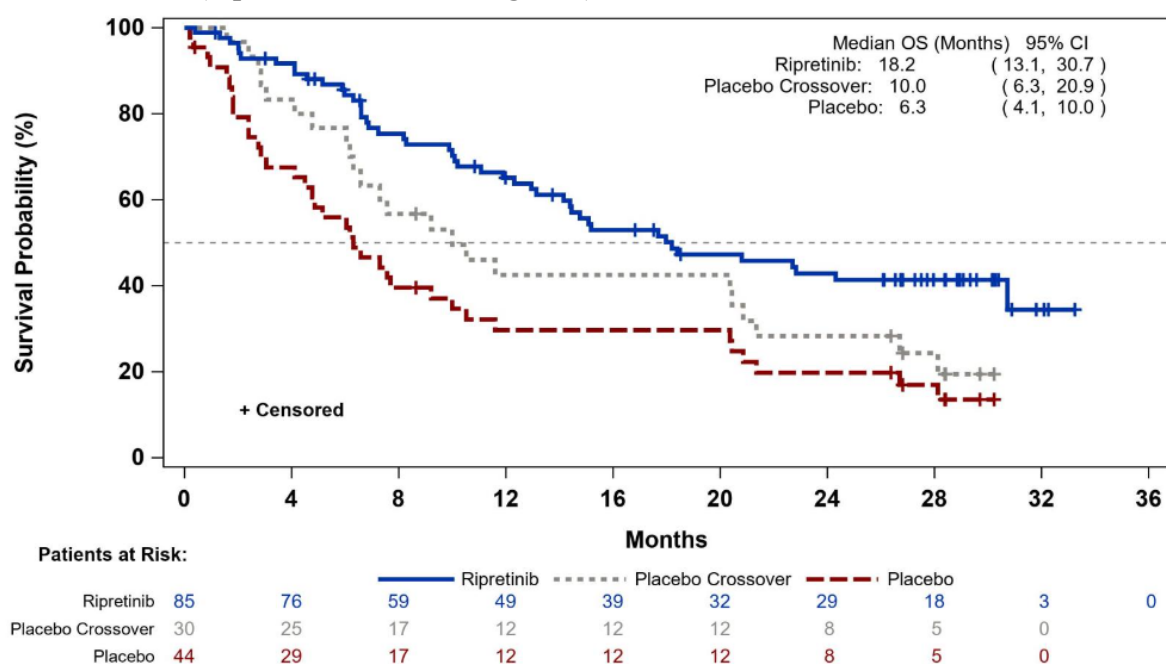
From the analysis of more mature OS data (January 2021 DCO; see Table 10), the estimated median OS for the ripretinib group was 18.2 months (95% CI: 13.1 to 30.7) (Figure 8). The median OS for the placebo group remained at 6.3 months (95% CI: 4.1 to 10.0). The HR for OS was 0.41 (95% CI: 0.26 to 0.65). Given that the January 2021 DCO is used to inform survival outcomes informing the company's economic analysis, further details are summarised in Section 4.4.3.3.

Table 10: OS in INVICTUS

Analysis set	DCO	N Ripr	N Pbo	Median OS, months		HR (95% CI)	Reference in CS
				Ripr	Pbo		
ITT	May 2019	85	44	15.1	6.6	0.36 (0.21 to 0.62)	Section 2.6
	March 2020	85	44	Not reached	6.3	0.42 (0.26 to 0.67)	Section 2.6
	January 2021	85	44	18.2	6.3	0.41 (0.26 to 0.65)	Section 2.6
Patients crossing over from placebo to ripretinib	May 2019	-	29	-	11.6	-	CS Section 2.6 and CS Appendix C
	January 2021	-	30	-	10.0	-	CS Section 2.6
Placebo patients who did not cross over	May 2019	-	15	-	1.8	-	CS Section 2.6 and CS Appendix C
	January 2021	-	■	-	■	-	TA881 clarification response, ⁴² question A9

Ripr - ripretinib; pbo - placebo; CI - confidence interval; HR - hazard ratio; ITT - intention-to-treat; OS - overall survival; CS - company's submission; DCO - data cut-off

Figure 6: Kaplan-Meier plot of OS with extended follow-up, January 2021 DCO (reproduced from CS, Figure 8)



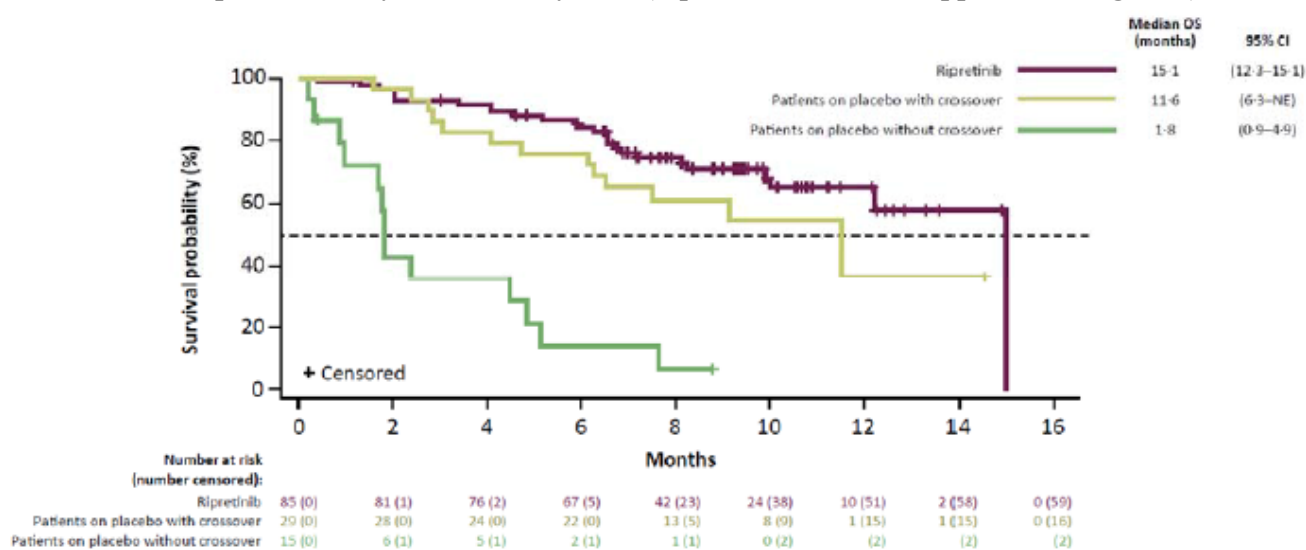
CI - confidence interval; OS - overall survival; DCO - data cut-off

Source: von Mehren et al. 2021,⁴⁴ slide 13 (presented at ESMO, September 16-21, 2021)

OS for patients crossing over, or not crossing over, from placebo to ripretinib

In *post hoc* analyses (see Figure 7), median OS in the 29 patients who crossed over from placebo to ripretinib was 11.6 months (May 2019 DCO) or 10.0 months (January 2021 DCO). Median OS in the 15 placebo patients who did not cross over was 1.8 months (May 2019 DCO) [REDACTED] (January 2021 DCO; from clarification response to TA881,⁴² question A9; see Figure 8).

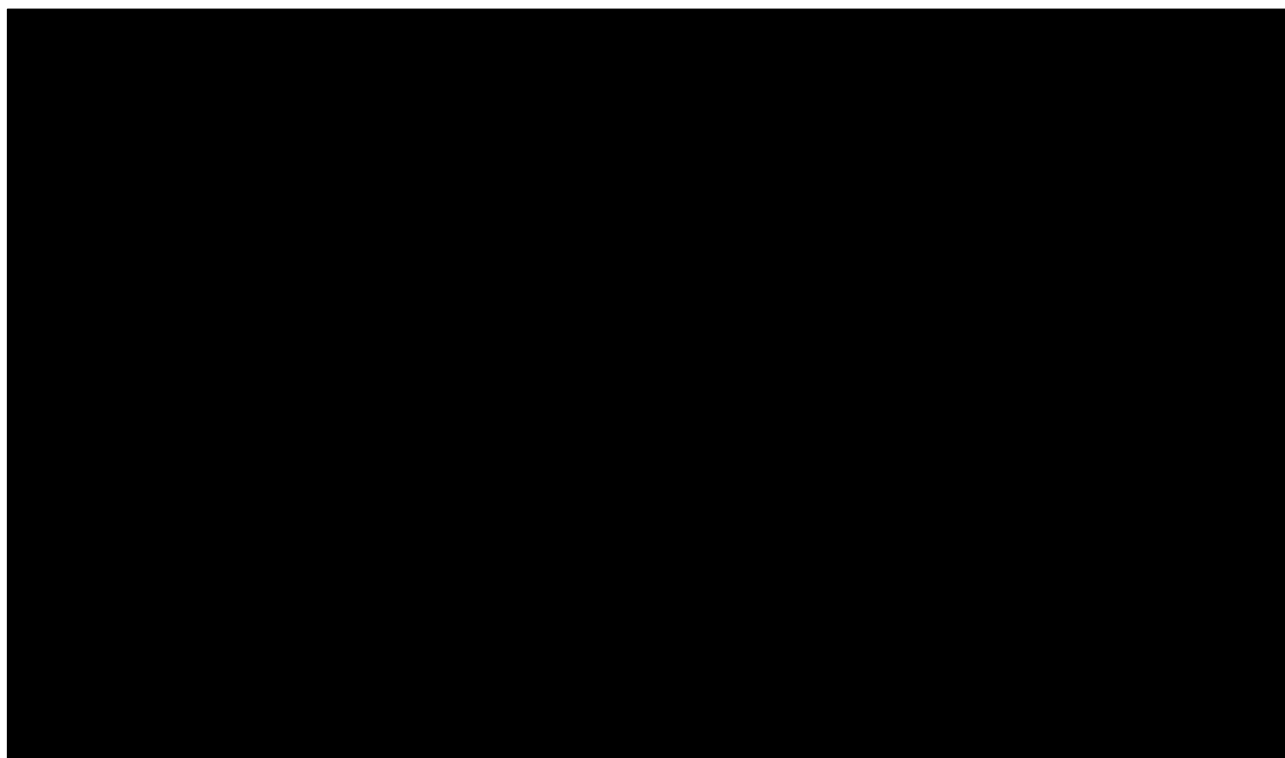
Figure 7: OS with crossover to ripretinib 150mg QD following disease progression on BICR – *post hoc* analysis, DCO May 2019 (reproduced from CS Appendix C, Figure 6)



BICR - blinded independent central review; CI - confidence interval; NE - not estimable; OS - overall survival; QD - once daily

Source: Blay et al. 2020³⁶

Figure 8: Kaplan-Meier plot of OS with extended follow-up, January 2021 DCO, including placebo patients who did not switch to ripretinib (reproduced from TA881 clarification response, question A9)



CI - confidence interval; OS - overall survival; DCO - data cut-off

3.3.2.1 OS post hoc analyses: OS after IPDE to ripretinib 150mg BID

The company conducted a series of *post hoc* analyses and consulted UK clinical experts at advisory board meetings to assess whether dose-escalating ripretinib from 150mg QD to 150mg BID after progression would affect OS (CS,³ Section 2.6.2: OS *post hoc* analyses: OS after IPDE to ripretinib 150mg BID). All of these analyses focused on patients who were randomised to the ripretinib arm of INVICTUS.²

Four analytic approaches were undertaken:

1. Open-label BID vs QD OS analysis
2. Censored BID-dosing analyses
3. Cox proportional hazards time-varying analysis
4. Two-stage adjustment.

Of the four analytic approaches, the open-label BID vs QD OS analysis was a naïve comparison of OS between mutually exclusive subgroups (i.e., patients who did versus did not receive dose escalation in the ripretinib arm) and was not included in the company's economic scenario analyses. In contrast, the remaining approaches employed various adjustment methods to estimate the direction and magnitude of the effect of post-progression dose escalation on OS, and their results were included in scenario

analyses using the company's economic model (see Section 4.2.5, Table 41). The company conducted several variations of each of the four approaches. The EAG has summarised these analyses in Table 11, based on CS,³ Section 2.6.2 and Table 15, and the company's responses to clarification questions B4 and B9.³⁵

Across the four analytic approaches, the evidence on the effect of post-progression dose escalation on OS was inconclusive. The advice received by the company from its clinical advisory board meetings suggested that the effect on OS is likely positive but not quantifiable. This broadly aligns with input received from the EAG's clinical advisors, who noted that dose escalation would typically be used in patients who are more likely to benefit and tolerate it.

Since these *post hoc* analyses ultimately aim to estimate (counterfactual) OS as if no dose escalation occurred – adjusting for subsequent treatments that would affect OS but are not expected to be used in practice (i.e., ripretinib 150mg BID, assuming this dosing regimen is not routinely commissioned) – the methods should align with those for treatment switching outlined in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 16,^{47, 48} with causal inference in mind. Specifically, methods such as inverse probability of censoring weighting (IPCW) and the two-stage estimation approach are better suited for adjusting for subsequent treatments that fall outside the original randomised treatments. For instance, adjusting the subsequent treatment from ripretinib 150mg BID to 150mg QD falls outside the original randomised comparison of ripretinib 150mg QD versus placebo. Other commonly used methods for treatment switching adjustment, such as the rank-preserving structural failure time model (RPSFTM) rely on the treatment effect between groups in the original randomised comparison. Hence, RPSFTM was deemed unsuitable in this context, and the EAG agrees that it was appropriate for the company not to explore this method for the IPDE adjustment in the ripretinib arm.

The EAG therefore considers the results from the company's two-stage approach to be the most appropriate among all of the *post hoc* analyses related to IPDE, which suggested that post-progression survival would likely “shrink” without dose escalation (CS³ Section 2.6.2, page 69 and clarification response,³⁵ question B9). This finding aligns with the views of the clinicians consulted by the company and the EAG. The IPCW adjustment was not pursued due to the small sample size in the INVICTUS trial; the EAG considers the company's decision not to apply this method to be reasonable.

The EAG provides a detailed critique of the *post hoc* analyses related to IPDE adjustment that were used to inform the company's economic scenario analyses (Analyses 2-4 in Table 11) in Section 4.2.5. It summarises all models fitted using the two-stage approach (Analysis 4 in Table 11) and explains why alternative methods (Analysis 2-3 in Table 11) are considered unsuitable. Analysis 1 ("Open-label BID

vs QD OS analysis") was not applied in the company's economic scenario analyses and is therefore described separately below.

A naïve comparison of OS between patients who received dose escalation and those who did not (Analysis 1(a) in Table 11; CS,³ Figure 9) showed a higher median OS of 18.4 months (95% CI 14.5 months to not estimable [NE]) for patients with IPDE versus 14.2 months (95% CI 7.2 months to NE) for those without IPDE. However, these results are not directly comparable because patients were not randomised to receive or not receive dose escalation. Additionally, selecting patients based on post-baseline characteristics introduces immortal time bias (i.e., patients who received dose escalation needed to survive long enough to receive it, whereas patients who did not could be receiving subsequent ripretinib 150mg QD treatment or discontinue treatment either before or after progression).

The company presented an additional naïve comparison (Analysis 1(b) in Table 11) which evaluated the time from first BID dosing to death for patients receiving dose escalation versus the time from first QD dosing (i.e., approximately at randomisation) to death for patients who did not receive dose escalation. This analysis suggested slightly better survival with QD dosing compared to BID dosing (CS,³ Figure 10). However, this comparison is misleading due to the use of different starting points: BID dosing can only begin at a later disease stage (after progression), which artificially disadvantages this group in the analysis.

Following concerns raised in the EAG's clarification letter³⁵ (question B3), the company conducted an updated naïve comparison (Analysis 1(c) in Table 11). This analysis compares post-progression survival (i.e., time from disease progression to death) between patients who received dose escalation and those who did not, which showed a non-statistically significant improvement in post-progression survival for patients receiving BID dosing. This finding may be partly explained by the higher proportion of patients with ECOG PS 0 at the time of progression among those who received dose escalation within the ripretinib arm (see clarification response,³⁵ Table 9). This is consistent with the EAG's clinical advisors' view that BID dosing would typically be offered to fitter patients who are more likely to tolerate and benefit from it. Nevertheless, since post-progression treatments were not randomised, the analysis cannot reliably estimate the causal effect of dose escalation among patients with comparable characteristics upon disease progression.

In summary, the company's naïve comparisons in Analyses 1(a)–1(c) (Table 11) provide insights into unadjusted survival among patients who underwent IPDE but cannot support causal conclusions due to the presence of important biases, including the lack of randomisation, differing treatment start times, and immortal time bias.

Table 11: Summary of analyses quantifying the effect of IPDE on OS conducted by the company

Analysis	Variation	Used in company's economic scenario analysis?
1. Open-label BID vs QD OS analyses	(a) Comparison of (CS, Figure 9): - OS of patients who received dose escalation - OS of patients who did not receive dose escalation	No
	(b) Comparison of (CS, Figure 10): - Time from first BID dosing to death for patients who received dose escalation - Time from first QD dosing (approximately at randomisation) to death for patients who did not receive dose escalation	
	(c) Comparison of (clarification response, Figure 4): - Time from disease progression to death of patients who received dose escalation - Time from disease progression to death of patients who did not receive dose escalation	
2. Censored BID-dosing analyses	(a) Comparison of (CS, Figure 11): - OS in the ripretinib arm: unadjusted - OS in the ripretinib arm with patients censored at the start of BID dosing	No
	(b) Comparison of OS between the following two non-mutually exclusive subgroups (CS, Figure 12): (i) Patients with progressed disease who escalated to ripretinib 150mg BID, combined with those without disease progression (ii) Patients with progressed disease who did not escalate to ripretinib 150mg BID, combined with those without disease progression	Yes (CS, Table 34) According to the company's clarification response B6, the "Open-label BID vs QD OS" analyses reported in the company's economic scenario analyses (CS, Table 60) corresponds to this approach.
3. Cox proportional hazards time-varying analysis	Cox proportional hazards models for OS with time-varying covariates (CS, Section 2.6.2, page 68):	-
	(1) Model 1: Included only ripretinib IPDE as the time-varying covariates	Yes (CS, Table 35)
	(2) Model 2: Included ripretinib IPDE, progression status, ECOG, EQ-5D VAS, lesion diameter sum, and percent change from baseline as the time-varying covariates	No (CS, Table 35)
	(3) Model 3: Included all covariates in Model 2, plus baseline lesion diameter sum, age, sex, race, region, baseline BMI, hepatic impairment, number of prior therapies, baseline creatinine clearance, and baseline renal impairment as the time-varying covariates	Yes (CS, Table 35)

Analysis	Variation	Used in company's economic scenario analysis?
4. Two-stage adjustment	A two-stage estimation was used to estimate counterfactual OS, assuming all patients that continued treatment post-progression and had not received dose escalation (CS, Section 2.6.2, p.69 and clarification response B9):	-
	(1) Simple model: adjusted only for time to progression.	Yes (CS, Table 36, clarification response B9)
	(2) Complex model: adjusted for time to progression, ECOG performance status at progression, EQ-5D VAS score at progression, and baseline age.	

QD - once daily; BID - twice daily; CS - company's submission; EQ-5D - Euroqol 5-Dimensions; VAS - visual analogue scale; OS - overall survival; BMI - body mass index; ECOG - Eastern Cooperative Oncology Group

3.3.3 Response rates

Objective responses in the double-blind period occurred in 8 of 85 patients (9%) in the ripretinib group and 0% of patients in the placebo group, at the May 2019 DCO (see Table 12). All responses were partial; there were no complete responses (CRs). Compared with placebo, a higher proportion of ripretinib patients had stable disease (SD) at 6 weeks (66% versus 20%) and 12 weeks (47% vs 5%).¹⁵ Fewer patients in the ripretinib group had disease progression (19% versus 64%) compared with the placebo group. At the March 2020 and January 2021 DCOs, objective response rates (ORRs) were 11.8% for ripretinib and 0% for placebo. The August 2020 DCO (reported in the SmPC²¹) reports the same ORR results as those observed in March 2020 and January 2021.

Table 12: Response data for INVICTUS, May 2019 DCO (adapted from CS, Table 16)

Response	Ripretinib (n=85): n (%)	Placebo (n=44): n (%)	p-value
Confirmed ORR	8 (9%)	0 (0%)	0.0504
CR	0 (0%)	0 (0%)	-
PR	8 (9%)	0 (0%)	-
SD (6 weeks)	56 (66%)	9 (20%)	-
SD (12 weeks)	40 (47%)	2 (5%)	-
PD	16 (19%)	28 (64%)	-
Not evaluable	4 (5%)	3 (7%)	-
No response assessment	1 (1%)	4 (9%)	-
Median duration of response	Not reached	N/a	

BICR - blinded independent central review; CI - confidence interval; CR - complete response; ITT - intention-to-treat; OR - objective response; ORR - objective response rate; PD - progressive disease; PR - partial response; SD - stable disease; N/a - not applicable

Source: Blay et al. 2020,³⁶ page 929, Table 2.

3.3.4 Other secondary endpoints

Duration of response (DoR), TTP, and time to best response are descriptive endpoints which were not tested for statistical significance due to insufficient power.

Time to best response

Median time to best response in the ripretinib group at the May 2019 DCO was 1.9 months (IQR 1.0 to 2.7 months). No patients in the placebo group achieved a response.

DOR

Median DOR in the ripretinib group was not reached at the May 2019 DCO and was 14.5 months at the January 2021 DCO.

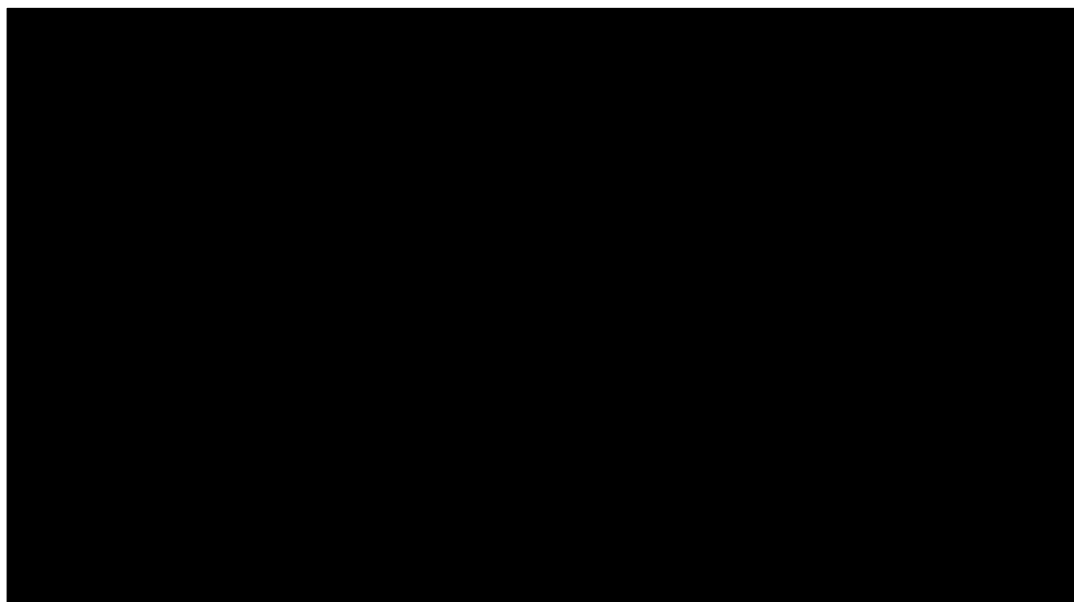
TTP

At the May 2019 DCO, median TTP was longer in the ripretinib group than the placebo group: 6.4 months (95% CI 4.6 to 8.4 months) vs 1.0 month (95% CI 0.9 to 1.7 months).³⁶ A TTP event occurred in 54.1% of patients (46/85, 39 censored) in the ripretinib group compared with 72.7% (32/44; 12 censored) in the placebo group.⁴⁹

TTD

At the January 2021 DCO, median TTD for ripretinib (any dose) during the double-blind and open-label periods was [REDACTED] (see Figure 9).

Figure 9: Kaplan-Meier curve for TTD for patients randomised to ripretinib in INVICTUS (reproduced from CS, Figure 13)



CI - confidence interval; TTD - time to discontinuation

Source: Deciphera Pharmaceuticals Data on File. Ripretinib post hoc TTD analysis. 25 July 2024

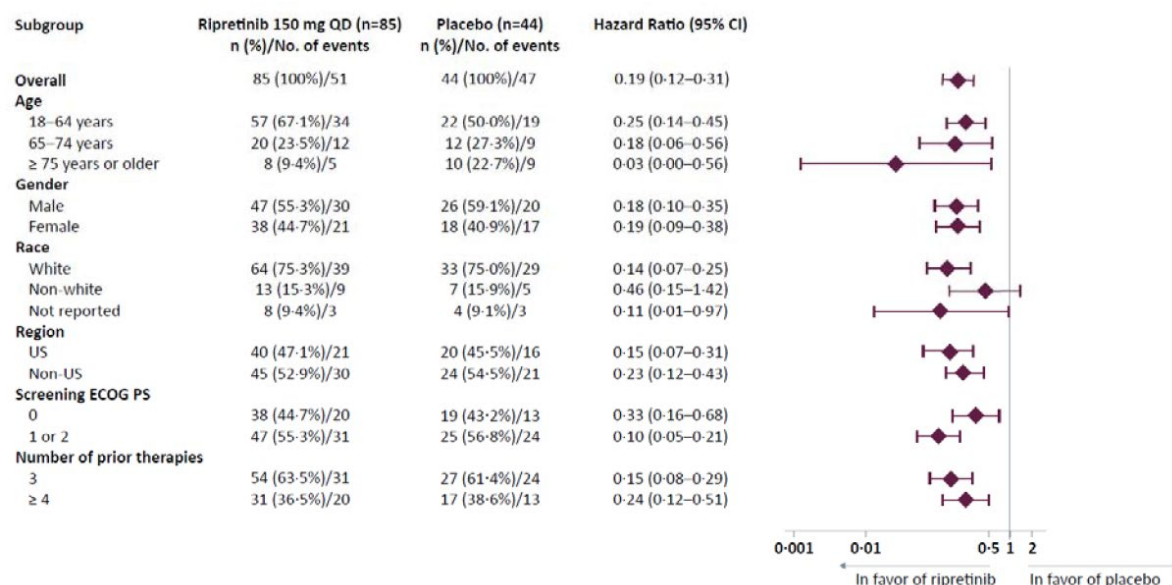
The CS³ notes that, on average, patients remained on ripretinib for [REDACTED] months after radiological progression (CS,³ Figure 13). Of the patients randomised to the ripretinib arm, 74% entered the open-label period and continued ripretinib.³⁶ The CS³ also states that the proportion of patients remaining on treatment after progression and the duration of treatment beyond progression reflects expected UK clinical practice.^{28, 36} Clinicians at a UK advisory board indicated that they would expect approximately 80% of patients to remain on ripretinib treatment post-progression. The EAG's clinical advisors agreed that they would continue to offer ripretinib beyond disease progression if patients were still deriving clinical benefit but considered that an 80% continuation rate was relatively high. The median duration of treatment with ripretinib 150mg BID was 3.7 months (range: 1 day to 18.6 months) and 11 of 43 patients (26%) were treated at this dose for 6 months or longer.³²

3.3.5 Subgroup analyses for PFS, OS and ORR

PFS: Subgroup analyses for PFS are reported in CS³ Section 2.8 and CS Appendix C;²⁹ these are reproduced in Figure 10. These analyses were pre-specified. Results were generally consistent across subgroups, though the small number of patients in some subgroups limits the interpretation of these analyses. The CS³ states that the UK advisory board 2024⁴⁰ did not consider age or line of therapy to be treatment effect modifiers. The EAG's clinical advisors agreed with this view. In addition, the CS³

also stated that the PFS subgroup analyses for the January 2021 DCO showed consistent results with the May 2019 DCO. However, data from January 2021 DCO were not provided in the CS.

Figure 10: PFS in patient subgroups as assessed by BICR, ITT population, May 2019 DCO (reproduced from CS, Figure 21)



BICR - blinded independent central review; CI - confidence interval; ECOG - Eastern Cooperative Oncology Group; PS - Performance Status; ITT - intention-to-treat; PFS - progression-free survival; QD - once daily.

Note: The number (% of total patients) of patients in each treatment group along with the number of events for each subgroup is presented.

Source: Blay et al. 2020.³⁶

The EAG notes that the subgroup analyses of PFS in INVICTUS suggests that the treatment effect for ripretinib in patients with ECOG PS 0 was less than that in patients with ECOG PS 1–2 (see Figure 10). In addition, older patients appear to have experienced a greater treatment effect. These results appear counterintuitive, and they contrast with the views of the UK advisory board. The company’s clarification response³⁵ (question A7) states that: “the findings of the subgroup analysis suggest that ripretinib provides benefit across all subgroups; however, the subgroups analysed were not large enough to support any further conclusions. Additionally, subgroup analyses consider a single variable in isolation and there may be other imbalances in baseline characteristics between subgroups that drive these counterintuitive results. The company’s response also states “....the higher proportion of patients with KIT exon 11 mutations in the ECOG PS 1-2 and older subgroups vs the ECOG PS 0 and younger subgroup may have contributed to the counterintuitive results for the PFS subgroup analyses” (see Table 13).

The EAG’s clinical advisors considered this to be a plausible explanation. Specifically, KIT exon 11 mutations are the most common mutation type in the GIST population, whereas KIT exon 9 mutations tend to be more aggressive and are more frequently observed in younger patients, possibly because patients with exon 9 mutations have a lower likelihood of surviving to older age.⁵⁰ In contrast, older

patients, who are typically more frail and more likely to have an ECOG PS of 1-2, tend to have a lower prevalence of exon 9 mutations. This is indirectly reflected in the INVICTUS population shown in Table 13, whereby a higher percentage of KIT exon 11 mutations is observed among older patients and those with ECOG PS 1-2, suggesting a likely lower proportion of exon 9 mutations in these subgroups.

Given that ripretinib may be more effective in patients with exon 11 mutations than in those with exon 9 mutations, this imbalance in mutation prevalence may partly explain the greater PFS benefit observed in both the older and ECOG PS 1-2 subgroups. However, due to the small sample sizes and lack of randomisation in these subgroup analyses, the findings should be interpreted with caution.

Table 13: Frequency of baseline KIT exon 11 mutations across patient subgroups at randomisation (patients randomised to ripretinib) (reproduced from clarification response, question A7)

Category	Ripretinib arm n (%)
Age subgroups	
18-64 years (n=57)	
≥65-74 years (n=20)	
75 years or older (n=8)	
ECOG PS subgroups	
0 (n=38)	
1-2 (n=47)	

ECOG PS - Eastern Cooperative Oncology Group performance status; KIT - Kit proto-oncogene; QD - once daily

In TA881,¹ the EAG requested data on PFS and OS subgroups according to whether patients had progressed on, were resistant to, or were intolerant to prior TKIs, as suggested in the final NICE scope.²⁰ However, the company responded that these data were not recorded (TA881 clarification response,⁴² question A8).

OS: Subgroup analyses for OS by age and line of treatment are shown in Table 14 (for the January 2021 DCO). The point estimate of the HR for OS was comparable across age groups. The relative treatment effect on OS appeared numerically more favourable for patients with 3 prior therapies than for those with ≥ 4 prior therapies.

Table 14: Subgroup analyses for OS, January 2021 DCO (reproduced from CS, Table 18)

Subgroup	Ripretinib vs placebo HR (95% CI)
Age	
18 - 64 years	0.42 (0.23 to 0.75)
65 - 74 years	0.46 (0.19 to 1.08)
75 years or older	0.41 (0.13 to 1.31)
Number of prior therapies	
3 prior therapies (n=54)	0.31 (0.18 to 0.54)
≥ 4 prior therapies (n=31)	0.63 (0.31 to 1.29)

HR - hazard ratio; CI - confidence interval

Source: NICE, Technology Appraisal Guidance [TA881], committee papers (unredacted)⁵¹

ORR: Subgroup analyses of ORR as presented in CS Appendix C,²⁹ are presented in Figure 11. ■

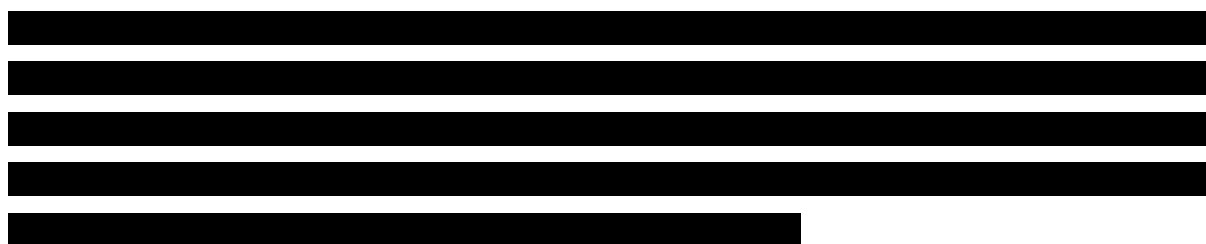
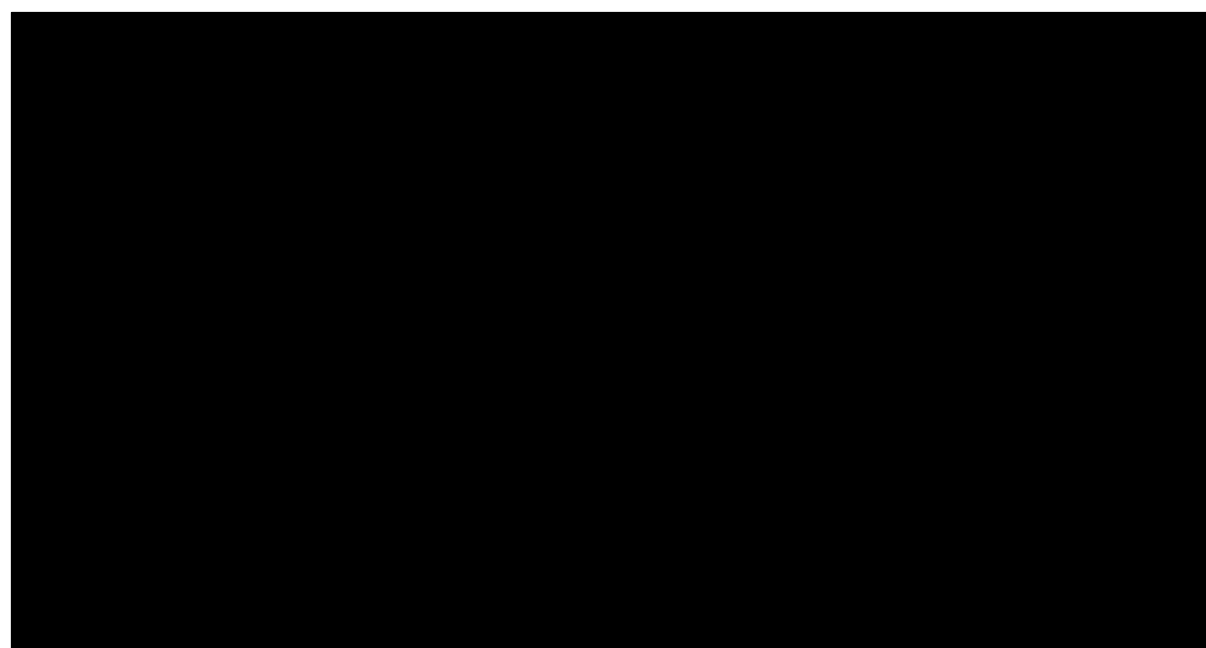


Figure 11: Forest plot of objective response rate based on IRR in patient subgroups, ITT Population (reproduced from CS Appendix C, Figure 5)



CI - confidence interval; DCC-2618 - ripretinib; ECOG - Eastern Cooperative Oncology Group; IRR - independent radiological review; ITT - intention-to-treat

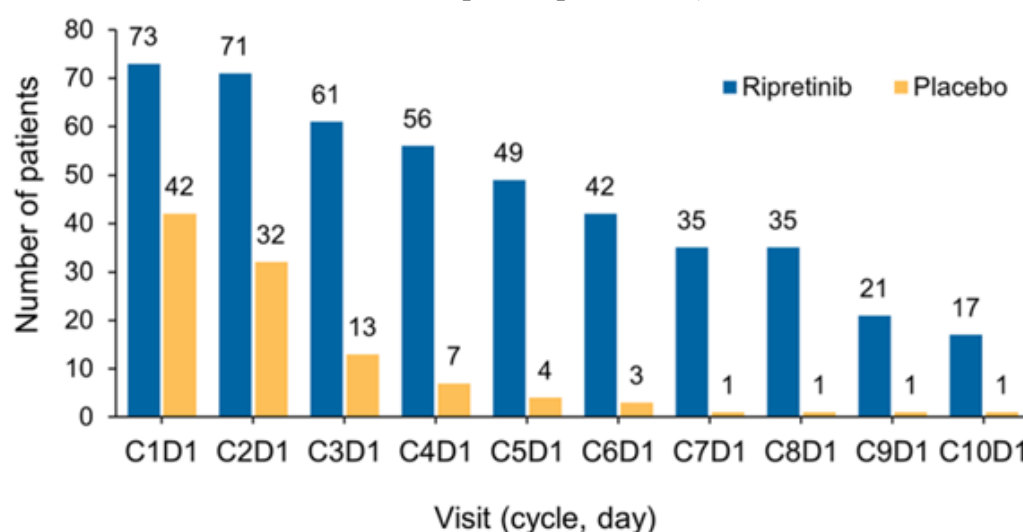
DCO: 31st May 2019

Source: Deciphera Pharmaceuticals. INVICTUS CSR, 2019.²

3.3.6 Health-related quality of life (HRQoL)

HRQoL in INVICTUS² was assessed using the EORTC QLQ-C30 role and physical functioning domains, the EQ-5D-5L questionnaire and the EQ-VAS from baseline to Cycle 2 Day 1 (i.e., the first 29 days of treatment). On Cycle 2 Day 1, 71 patients were evaluable in the ripretinib arm and 32 patients were evaluable in the placebo arm (CS,³ Section 2.6, page 74). The CS³ states that later measurements are not reported due to the low number of evaluable patients in the placebo group after this time point. In response to clarification question A4,³⁵ the company stated that due to rapid disease progression, the number of patients in the placebo arm was very low after Cycle 2 Day 1; hence, any statistical comparison across study arms after this time point would be highly uncertain (see Figure 12).

Figure 12: Number of patients with PRO assessment over time in INVICTUS (reproduced from clarification response, question A4)



C - cycle; D - day; PRO - patient-reported outcome

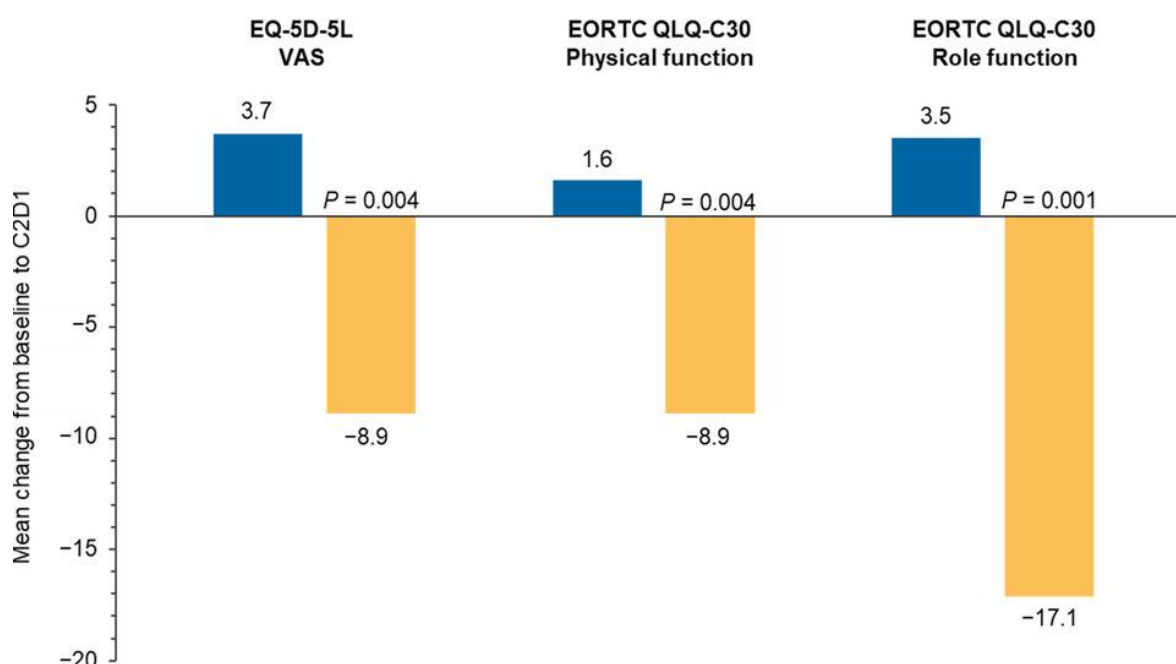
Each cycles had a duration of 28 days

Source: Schoffski et al., 2022⁵²

The CS³ states that patients in the ripretinib group reported an improvement in the physical and role functioning domains of the EORTC QLQ-C30 from baseline to Cycle 2 Day 1 (see Figure 13), with an adjusted mean increase in scores (indicating improvement) of 1.6 and 3.5 points, respectively, compared with a decline of 8.9 and 17.1 points for patients in the placebo group. Patients likewise reported an improvement in HRQoL from baseline to Cycle 2 Day 1, as assessed by an adjusted mean increase in EQ-VAS scores of 3.7 versus a decline of 8.9 with placebo. The CS³ states that no minimal clinically important difference (MCID) for HRQoL has been established in GIST, but that assuming a MCID of 10% mean score change or score change of 5 points, the difference between ripretinib and placebo could be considered clinically meaningful. The CS³ also reports the above HRQoL measures through to Cycle 10 in the ripretinib arm, but not the placebo arm. Patients treated with ripretinib appeared to remain stable on all scores for patient-reported outcome (PRO) measures through to Cycle 10 (see CS,³ Figure 15 and Table 17).

Patient demographic and baseline characteristics were generally well balanced between treatment arms in terms of stratification factors including ECOG PS and number of prior systemic anticancer treatments.² The adjusted mean change from baseline to Cycle 2 Day 1 in EQ-5D-5L utility score was -0.009 (standard error [SE] 0.020) for the ripretinib group and -0.06 (SE 0.028) for the placebo group (see CS,³ Table 17).²

Figure 13: HRQoL - change from baseline to Cycle 2 Day 1 in EQ VAS and EORTC QLQ C30 PRO measures, ITT population (reproduced from CS, Figure 14)



Legend: Ripretinib (Blue), Placebo (Yellow)

C2D1 - Cycle 2, Day 1; EORTC QLQ-C30 - European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-item; EQ-VAS - Euroqol visual analogue scale; ITT - intention-to-treat; PROM - patient-reported outcome measure

Note: p-values are nominal.

The physical and role function questions were rolled up to a score out of 100. Change from baseline to C2D1 in EQ-VAS scores were evaluable in 70 and 32 patients in the ripretinib and placebo arm, respectively. For the EORTC QLQ-C30 physical functioning, 71 and 32 patients were evaluable in each group, respectively, and for the EORTC QLQ-C30 role functioning, 70 and 32 patients were evaluable in each group, respectively.

Source: Schöffski et al. 2022⁵²

Time until definitive deterioration, decline in the PRO measure that does not recover

At the August 2020 DCO, time until definitive deterioration (TUDD), which was defined as a clinically meaningful decline in the PRO measure that does not recover,³¹ was longer in patients receiving ripretinib compared with placebo.^{31, 52} For overall health, the median TUDD for the placebo group was 7.7 weeks; however, it had not been reached in the ripretinib group by 56 weeks. For EORTC QLQ-C30 (physical and role function) and EQ-VAS score, median TUDD was 41.6 weeks in the ripretinib group vs 7.9 weeks in the placebo group. Median TUDD was longer than median PFS (6.3 months) and median TTD with ripretinib (8.8 months) (see CS,³ Figures 16, 17 and 18). The EAG notes that HRQoL results are descriptive and were not formally tested, hence should be interpreted with caution.

3.4 Supporting evidence – the Royal Marsden expanded access study

As supporting evidence for the effectiveness of ripretinib, the CS³ includes details of the Royal Marsden expanded access study, which was undertaken independently by The Royal Marsden Hospital, London, UK.²⁸ Full details are provided in CS³ Section 2.3.4.

3.4.1 Study design

The Royal Marsden expanded access study is a single-arm retrospective observational study assessing the effectiveness and safety of ripretinib in a cohort of patients treated in a real-world setting. Study details are presented in Table 15. Study eligibility criteria are reported in Table 10 of the CS.³ In summary, the study included patients with advanced (unresectable or metastatic) GIST who commenced ripretinib at the Royal Marsden Hospital between January 2020 and October 2021; patients had to have had imaging available for retrospective assessment of radiologic response according to mRECIST version 1.1, and had to have at least one measurable lesion. Radiological assessments were performed every 10–14 weeks or when clinically indicated. Patients remained on treatment until clinical benefit was no longer observed or until unacceptable toxicity was seen.²⁸

The EAG notes that the Royal Marsden expanded access study included patients who had received two or more prior lines of treatment; as such this study does not fully align with the population defined in the final NICE scope,²⁰ the MHRA marketing authorisation²¹ or the population in the INVICTUS trial,³ each of which relates to adults with advanced GIST who have received prior treatment with three or more TKIs, including imatinib.

Table 15: Summary of the Royal Marsden expanded access study with ripretinib (reproduced from CS, Table 9)

Study	Expanded access program use of ripretinib (DCC-2618) for the treatment of patients with advanced GIST (NCT04148092)
Study design	Retrospective observational single centre cohort
Population	Patients with unresectable or metastatic GIST and available clinical and radiological data, who had received at least two prior lines of treatment
Intervention(s)	Ripretinib
Comparator(s)	N/a
Reported outcomes	PFS, TTD, ORR, TBP, OS, AEs

AE - adverse event; GIST - gastrointestinal stromal tumour; ORR - overall response rate, OS - overall survival; PFS - progression-free survival; TBP - treatment beyond progression; TTD - time to treatment discontinuation.

Source: Lim et al. 2024.²⁸

Patients received a starting dose of ripretinib 150mg QD but were given the opportunity to dose-escalate to 150mg ripretinib BID at the time of disease progression, as determined by their treating physician. Patients were retrospectively assessed as two groups: (i) those receiving 150mg ripretinib QD and (ii) those with dose escalation to 150mg ripretinib BID upon tumour progression.²⁸

Outcomes

The following outcomes were reported for the DCO of the 15th January 2023²⁸

- *PFS QD*: The time from the date of the first 150mg ripretinib QD dose to the time of progression or death²⁸ (equivalent to PFS in INVICTUS²).

- *PFS BID*: The subgroup of patients undergoing IPDE, defined as the time from date of the first 150mg ripretinib BID dose to the time of progression or death (equivalent to PFS2 in INVICTUS).
- *PFS ITT*: The overall duration of ripretinib treatment regardless of dosage (no equivalent end point in INVICTUS).
- *ORR*: Confirmed CR or PR.
- *TTD*: Time from the first day of ripretinib treatment (at a specified dose) to the last day of ripretinib treatment (at a specified dose) regardless of the cause of treatment discontinuation. Defined for the same groups as PFS endpoints.
- *TBP*: Ripretinib treatment beyond disease progression.
- *OS*: Time from the date of the first 150mg ripretinib QD dose to the time of death from any cause.

Retrospective mRECIST measurements were used to assess PFS, best ORR and time to best response.

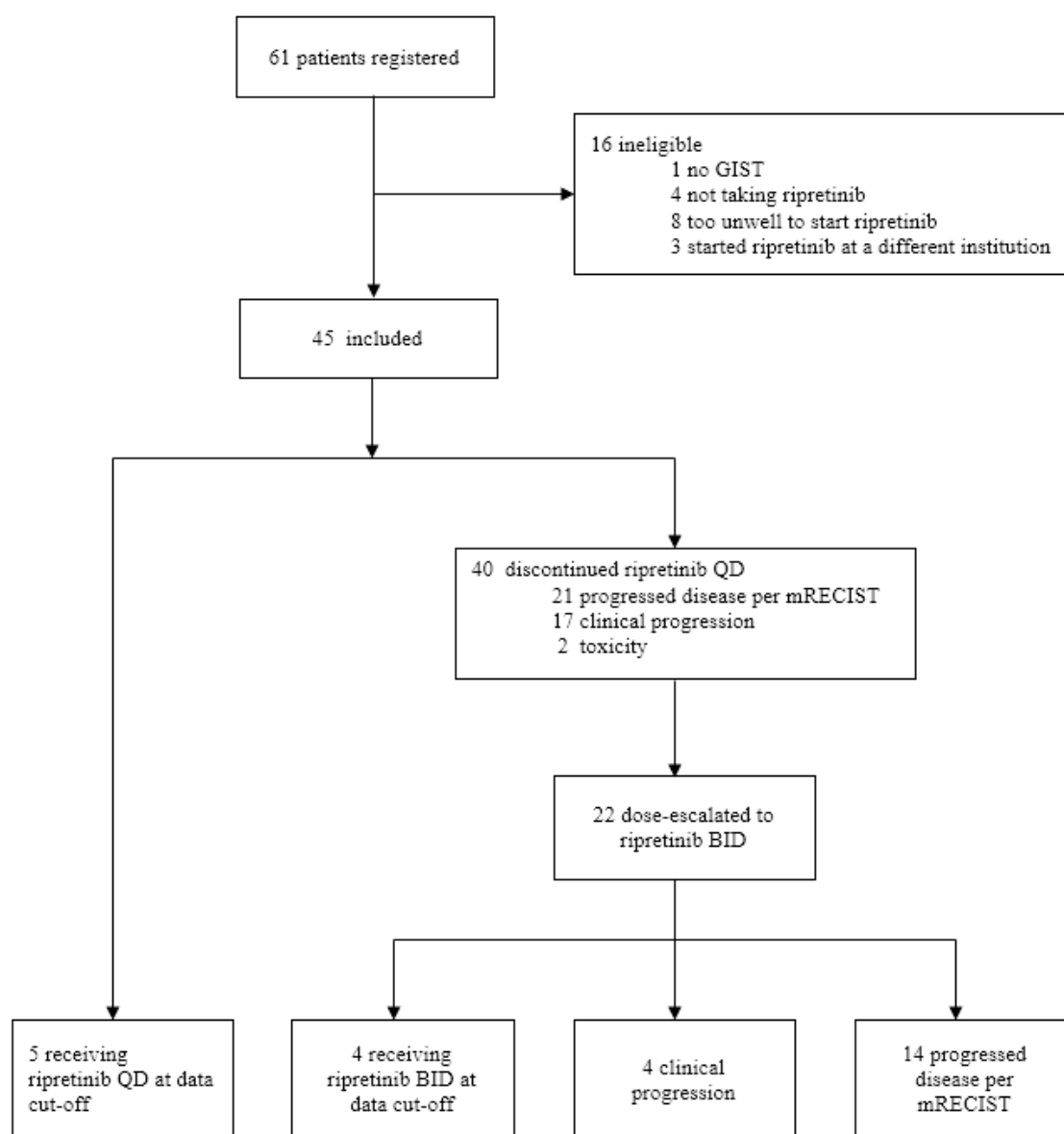
Study quality

Following a request from the EAG, the company conducted a quality assessment of the Royal Marsden expanded access cohort study (see clarification response,³⁵ question A8) using the CASP Cohort Study Checklist. The CS³ highlights that as a non-randomised, non-controlled retrospective study, the Royal Marsden study has inherent limitations affecting the statistical validity of its results. Such retrospective studies are prone to issues including limited or missing data, less rigorous data collection (due to the absence of a pre-specified analysis plan or study protocol) and potential recall bias.

3.4.2 Patient baseline characteristics

Of the 61 patients registered for the ripretinib expanded access programme at the Royal Marsden Hospital, 16 patients were excluded (see Figure 14). Overall, 45 patients with available clinical and radiological data were included in the study.²⁸

Figure 14: Flow of participants in The Royal Marsden expanded access study, DCO January 2025



Baseline patient characteristics are reported in Table 16. Information on primary mutational status was not available for 6 patients, and the small bowel was the most common primary tumour site (51.1%). All but one patient had metastatic disease. All patients had progressed after imatinib and 95.6% of patients had also progressed after sunitinib. Some baseline characteristics of patients in the Royal Marsden expanded access study²⁸ differed from those in INVICTUS.² Patients in the Royal Marsden cohort were older (median age 62 vs. 59 years), had higher prevalence of KIT exon 11 mutation (73.3% vs. 64%), and had poorer PS at baseline with 98% having an ECOG score of 1 and 2 compared to 56% in INVICTUS. Additionally, 42% of patients in the Royal Marsden study had received only two prior lines of treatment before initiating ripretinib. The EAG requested that the company provide data that reflect the subgroup with three prior lines of treatment to enable a more appropriate comparison with

the population relevant to this appraisal (see clarification response,³⁵ question A9). The company's response states that this re-analysis was not possible because the company does not hold relevant individual patient data (IPD) for the Royal Marsden study as it was investigator-led. However, the company's response notes that in the univariate and multivariate Cox regression models, the number of previous lines of treatment (2 versus 3 or more) was not associated with a significant difference in PFS (QD or ITT) or OS (see CS,³ Section 2.8.2). Despite the company's clarification, the EAG notes that 42% of patients in the Royal Marsden Study are outside the scope of this appraisal; hence, the data should be interpreted with caution.

Table 16: Patient baseline characteristics in the expanded access cohort, Royal Marsden, UK (reproduced from CS, Table 11)

Total Number of Patients	45	100%
Sex		
Female	19	42.2%
Male	26	57.8%
Age		
Median, Q1–Q3	62	57–72*
Primary mutational status		
KIT exon 11	33	73.3%
KIT exon 9	3	6.7%
PDGFRA	3	6.7%
N/A	6	13.3%
Primary tumour site		
Stomach	13	28.9%
Small bowel	23	51.1%
Other	9	20.0%
Stage		
Locally advanced	1	2.2%
Metastatic	44	97.8%
1 site	15	34.1%
2 sites	18	40.9%
3 or more sites	11	25.0%
ECOG PS		
0	1	2.2%
1	42	93.3%
2	2	4.4%
Number of previous lines		
2	19	42.2%
3 or more	26	57.8%
Previous lines		
Imatinib	45	100%
Sunitinib	43	95.6%
Regorafenib	24	53.3%
Avapritinib	13	28.9%

ECOG PS - Eastern Cooperative Oncology Group Performance Status; Q - quartile

Source: Lim et al. 2024.²⁸

* Interquartile range

The CS³ notes that although there was an unusually high prevalence of small bowel GIST in the included patients, this is unlikely to have had a major impact on the results, as the site of tumour origin was not associated with PFS or OS in multivariate analyses. The CS also states that patients in the Royal Marsden study were from a single institution; hence, they would not be expected to be completely representative of the advanced GIST patient population in the UK.

3.4.3 *Summary of clinical effectiveness - Royal Marsden expanded access study*

3.4.3.1 Patient disposition

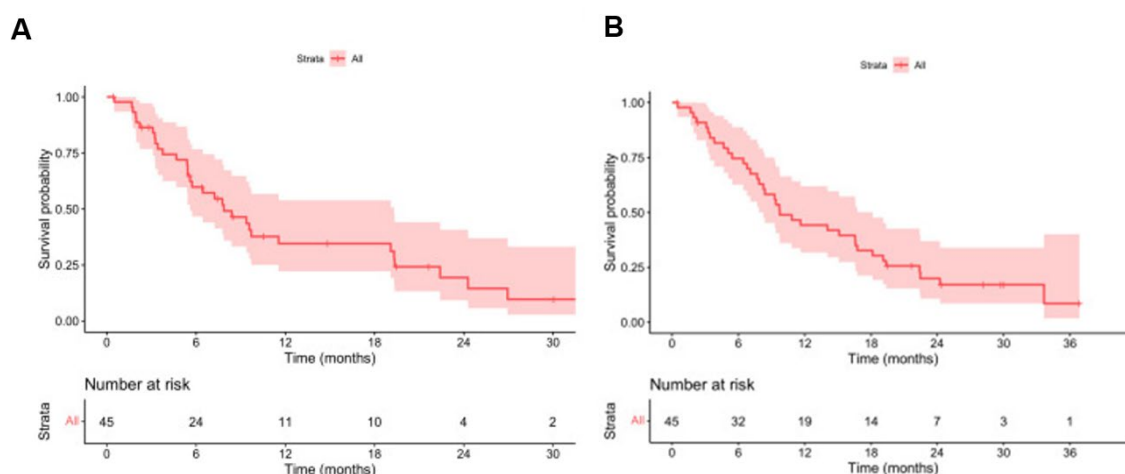
The median follow-up time was 24.2 months (95% CI 19.7 to 29.7 months). At the January 2025 DCO, 5 (11.1%) patients were still receiving 150mg ripretinib QD and 40 (88.9%) patients discontinued ripretinib QD due to: mRECIST (radiological) PD in 21 (46.7%) cases, clinical PD (defined as worsening patient-reported symptoms in the presence of radiological signs of PD that did not reach the level required for confirming mRECIST PD) in 17 (37.8%) cases, and toxicity in 2 (4.4%) cases. Of the 21 patients with mRECIST PD, 15 dose-escalated to ripretinib BID and 6 did not dose-escalate (2 received another TKI, and 4 declined IPDE and were referred back to their local team). Of the 17 patients with clinical PD, 10 were too unwell to continue treatment and 7 dose-escalated to ripretinib BID. In total, 22 (48.9%) patients had their dose escalated to ripretinib 150mg BID (see Figure 14).

Of the 22 patients undergoing IPDE, 4 (18.2%) were still receiving ripretinib BID at the time of the DCO, 4 (18.2%) had clinical progression and 14 (63.6%) had mRECIST PD. Four patients went on to receive a further line of treatment after progression on ripretinib BID. At the time of the DCO, 20 (44.4%) patients were still alive and 25 (55.6%) had died.²⁸

3.4.3.2 Progression-free survival

Median PFS for patients receiving ripretinib 150mg QD was 7.9 months (95% CI 5.6 to 19.3 months) (Figure 15A). Median PFS for patients receiving ripretinib 150mg BID (after initial disease progression) was 5.4 months (95% CI 2.8 to 9.3 months). The overall median PFS ITT was 9.7 months (95% CI 8.3 to 18.1 months) (see Figure 15). The CS³ notes that the median PFS achieved in INVICTUS² (6.3 months; 95% CI 4.6 to 8.1 months) was shorter than that reported for patients receiving ripretinib 150mg QD in the expanded access program, potentially due to the lower frequency of radiological assessment in clinical practice.⁴⁰ The EAG's clinical advisors considered this explanation to be plausible.

Figure 15: (A) Median PFS ripretinib QD (B) Median PFS ripretinib, ITT population, UK expanded access program (reproduced from CS, Figure 19)



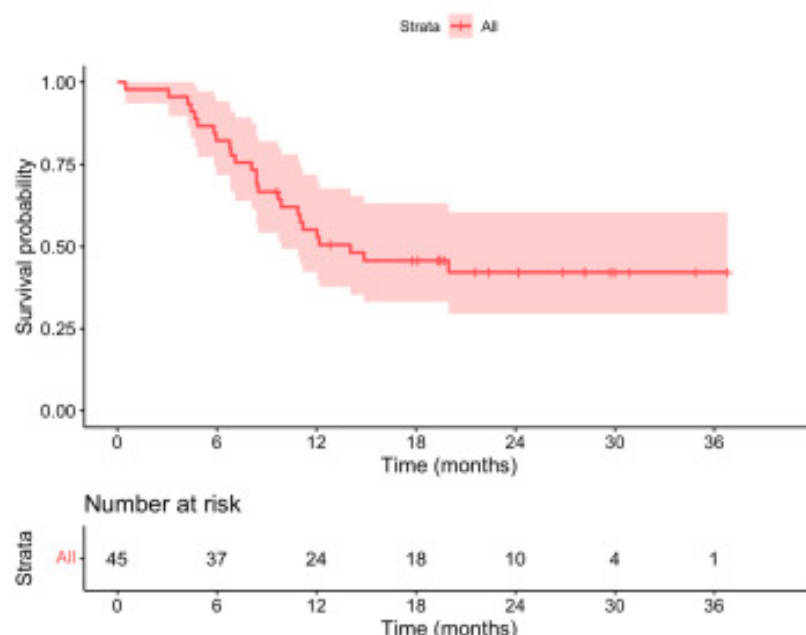
ITT - intention-to-treat, PFS - progression-free survival, QD - once daily, UK - United Kingdom
Source: Lim et al. 2024.²⁸

3.4.3.3 Overall survival

Median OS was 14.0 months (95% CI 9.9 months to NE), including all patients, irrespective of post-progression ripretinib dosing (see Figure 16). This was lower than the median OS achieved in INVICTUS² (18.2; 95% CI 13.1 to 30.7 months) after a similar median follow-up period.^{28, 36} The company stated that the OS achieved in clinical practice is often lower than that achieved in clinical trials due to the ‘controlled by protocol’ nature of a clinical trial, i.e., stringent recruitment criteria, intensive patient care with close monitoring and contact maintained throughout the study.

Patients in the Royal Marsden study had poorer PS at baseline compared with those in INVICTUS (ECOG PS 1-2 98% vs 56%, respectively).^{28, 36} The EAG’s clinical advisors and the UK clinical advisory panel confirmed that ECOG PS is a key treatment effect modifier in this patient population.^{40, 53-55} However, it should also be noted that 42.2% of the patients received ripretinib as a third-line treatment (these patients are outside of the scope of the appraisal and the marketing authorisation for ripretinib).

Figure 16: Median OS ripretinib, ITT population, UK expanded access program (reproduced from CS, Figure 20)



Source: Lim et al. 2024.²⁸

3.4.3.4 Objective response rates

The best responses to ripretinib 150mg QD were PR in 7 of 42 patients (16.7%) and SD in 29 of 42 patients (69.0%). Median time to best response was 2.6 months (IQR 1.9–3.3 months). Three patients did not undergo radiologic evaluation whilst receiving ripretinib QD due to rapid clinical deterioration. The best responses to ripretinib 150mg BID were PR in 2 of 20 patients (10.0%) and SD in 9 of 20 patients (45.0%). Three patients did not undergo radiologic evaluation whilst on ripretinib BID (2 patients due to rapid clinical deterioration and 1 patient was dose-escalated 2 weeks before the DCO).²⁸

3.4.3.5 Time to discontinuation and treatment beyond progression

The CS³ reports that median TTD was similar to median PFS in patients receiving ripretinib 150mg QD at 7.1 months (95% CI 5.8 to 11.0 months). Post-progression ripretinib 150mg QD was recorded for 14 patients (31.1%) and the median duration of treatment beyond progression (TBP) was 1.9 months (IQR 1.0 to 3.0 months). The CS³ notes that patients with TBP generally showed no significant differences in baseline characteristics compared with patients without TBP, apart from site of disease and that this difference was most likely due to the small sample size.

Median TTD in patients receiving ripretinib 150mg BID was 6.5 months (95% CI 4.6 to 10.7 months). Ripretinib BID TBP (treatment beyond second disease progression) was observed in 6 patients (27.3%). The median duration of TBP was 2.8 months (IQR 1.0 to 5.4 months).²⁸

3.4.3.6 Subgroup analyses

The CS³ reports that in multivariate Cox regression models, the absence of a KIT exon 11 mutation was associated with a statistically significant reduction in PFS QD (HR 4.67, 95% CI 1.53 to 14.29), PFS ITT (HR 3.06, 95% CI 1.08 to 8.67) and OS (HR 4.19, 95% CI 1.49 to 11.82) compared to when a KIT exon 11 mutation was present. Patients with three or more metastatic sites had statistically shorter PFS ITT compared with patients with less than two metastatic sites (HR 3.00, 95% CI 1.05 to 8.57). Other variables tested, including number of previous lines of treatment (2 vs 3 or more) and age, were not associated with significant differences in PFS (QD or ITT) or OS.²⁸

3.5 Safety of ripretinib

3.5.1 Studies providing safety data on ripretinib

The CS³ (Section 2.11) focuses on safety data from the INVICTUS RCT.² The reported safety data are for the double-blind period of INVICTUS (i.e., up to disease progression), therefore the EAG notes that these data should not be affected by treatment switching after progression. The safety population included all 85 patients randomised to ripretinib and 43 of 44 patients randomised to placebo (i.e., a total of 128 of 129 randomised patients).

In terms of other sources of safety data on ripretinib, the company identified two studies; a Phase 1 single-arm study of GIST patients treated with ripretinib at a dose of 150mg either QD or BID (NCT02571036)^{34,39} and a Phase 2 single-arm study of adults with advanced GIST who had progressed on prior three or more TKIs (NCT04282980).^{37,38} The company provided no further details apart from stating in CS Appendix D²⁹ that the safety results of the Phase 2 and Phase 1 single-arm studies were broadly aligned with those of INVICTUS.² In addition, the company included safety data from the Royal Marsden expanded access study²⁹ and undertook a pooled safety analysis of the INVICTUS study and the Phase 1 single-arm study (NCT02571036).^{34,39}

3.5.2 Summary of safety data from INVICTUS

A summary of safety data is provided in Table 17. The overall frequency of treatment-emergent adverse events (TEAEs) was similar for ripretinib and placebo (99% vs 98%), [REDACTED]

[REDACTED] At the January 2021 DCO, the frequency of Grade 3/4 AEs was slightly higher for ripretinib than placebo (49% vs. 44%) and [REDACTED]

[REDACTED] Serious adverse events (SAEs) were less frequent for ripretinib than placebo (31% vs. 44%), whilst drug-related SAEs were similar in both groups (9% vs. 7%). Any AEs leading to discontinuation were slightly less frequent for ripretinib than placebo (8% vs. 12%). However, treatment-related AEs leading to discontinuation (4.7% vs. 2.3%), dose reduction (5.9% vs. 2.3%) or dose interruption (14% vs. 7%) were more frequent for ripretinib.³

Table 17: Summary of TEAEs and treatment-related TEAEs in the double-blind phase of INVICTUS, safety population (adapted from CS, Tables 19 and 24)

Categories	Ripretinib (n=85), n (%)	Placebo (n=43)*, n (%)
All AEs		
Any TEAE	84 (99%)	42 (98%)
Any treatment-related TEAE		
***Any Grade 3/4 TEAE	42 (49%)	19 (44%)
Any Grade 3/4 treatment-related TEAE		
Any treatment-emergent SAE (>2%)	26 (31%)	19 (44%)
Any treatment-emergent drug-related SAE	8 (9%)	3 (7%)
Dose reductions and discontinuations		
***Any TEAE leading to treatment discontinuation	7 (8%)	5 (12%)
***Any TEAEs leading to dose reduction	8 (9%)	1 (2%)
***Any TEAEs leading to dose interruption	24 (28%)	10 (23%)
Any treatment-related TEAE leading to treatment discontinuation	4 (5%)	1 (2%)
Any treatment-related TEAE leading to dose reduction	5 (6%)	1 (2%)
Any treatment-related TEAE leading to dose interruption	12 (14%)	3 (7%)
Deaths		
Any death	12 (14%)	13 (30%)
***Any TEAE leading to death	6 (7%)	10 (23%)
Any treatment-related TEAE leading to death	1 (1%)	1 (2%)
Death	1 (1%)	0
Pulmonary oedema	0	1 (2%)**
Septic shock	0	1 (2%)**

TEAE - treatment-emergent adverse event

* 44 patients randomised to placebo; one did not receive treatment.

** Pulmonary oedema and septic shock were reported in the same patient. Source: Blay et al. 2020,³⁶

***Jan 2021 data cut-off Source: von Mehren, et al. 2021⁴⁴

3.5.3 Deaths

Deaths during the double-blind period were less frequent for ripretinib than placebo (14% vs. 30%) and were stated in the CS³ to be mainly due to disease progression (11 of 12 deaths in ripretinib arm);³⁶ see Table 17. AEs leading to death were less frequent for ripretinib than placebo (7% vs. 23%), whilst treatment-related AEs leading to death occurred in one patient in each group (1.2% vs. 2.3%). One death was due to unknown causes in the ripretinib group, and one death was due to septic shock and pulmonary oedema in the placebo group.

3.5.4 Treatment-emergent adverse events

Table 18 summarises TEAEs reported in ≥30% of patients receiving ripretinib in the QD period and the corresponding TEAEs post-IPDE to 150mg BID. The most common TEAEs observed of all grades were: alopecia; fatigue and abdominal pain. Although an increase in AEs was observed with dose escalation, these were mainly Grade 1 or 2 in severity.

Table 18: Treatment emergent adverse events reported in $\geq 30\%$ of patients with advanced GIST receiving ripretinib in the QD period and the corresponding TEAEs post IPDE to 150mg BID, August 2020 DCO (reproduced from CS, Table 20)

Categories	Ripretinib 150mg QD period (n=43), n (%)		Ripretinib 150mg BID period (n=43), n (%)*	
	All grades	Grade 3/4	All grades	Grade 3/4
Alopecia	26 (60%)	-	6 (14%)	-
Fatigue	19 (44%)	1 (2%)	7 (16%)	2 (5%)
Abdominal pain	18 (42%)	2 (5%)	13 (30%)	3 (7%)
Constipation	16 (37%)	0	8 (19%)	0
Myalgia	15 (35%)	1 (2%)	7 (16%)	0
Decreased appetite	13 (30%)	1 (2%)	11 (26%)	2 (5%)
Nausea	13 (30%)	1 (2%)	10 (23%)	1 (2%)

GIST - gastrointestinal stromal tumour; IPDE - intra-patient dose escalation; DCO - data cut-off; QD - once daily; BID - twice daily

- indicates where no data were captured regarding adverse event grade ratings

*Data represent new or worsening TEAEs in the ripretinib 150mg b.i.d. period. The ongoing TEAEs from the ripretinib 150mg QD period were not included if they remained at the same or lower grade

Source: Zalcberg, et al. 2021³²

Grade 3/4 TEAEs

At the January 2021 DCO, 49.4% of patients in the ripretinib group experienced a Grade 3/4 TEAE, compared with 44.2% of patients in the placebo group.⁴⁴ Grade 3/4 TEAEs occurring in $>3\%$ of patients are presented in Table 19.

Table 19: Summary of Grade 3/4 TEAEs in the double-blind phase, safety population, 15 January 2021 DCO (reproduced from CS, Table 19)

Categories	Ripretinib (n=85), n (%)	Placebo (n=43)*, n (%)
Grade 3/4 TEAE ($>3\%$)		
Anaemia	9 (11%)	6 (14.0%)
Abdominal Pain	6 (7%)	2 (5%)
Hypertension	6 (7%)	0
Hypophosphataemia	4 (5%)	0
Lipase increased	4 (5%)	0
Fatigue	3 (4%)	1 (2%)
Nausea	3 (4%)	0
Vomiting	3 (4%)	0

TEAE - treatment-emergent adverse event.

* 44 patients randomised to placebo; one did not receive treatment.

Source: von Mehren, et al. 2021.⁴⁴

Treatment-emergent SAEs

At the 31st May 2019 DCO, treatment-emergent SAEs that occurred in $>2\%$ of patients in the ripretinib arm were: abdominal pain (5% vs. 5%); anaemia (4% vs. 2%); nausea (2% vs 0%) and vomiting (2% vs. 0%). Deaths due to SAEs occurred in 3 of 85 patients (4%) in the ripretinib arm and 4 of 43 patients (9%) in the placebo arm. The CS does not present updated data on treatment-emergent SAEs from later DCOs.

3.5.5 Treatment-related TEAEs

The most common treatment-related TEAEs ($\geq 20\%$) in the ripretinib arm were: alopecia (49%); myalgia (28%); nausea (26%); fatigue (26%) and palmar-plantar erythrodysesthesia syndrome (PPES) (21%). The majority were Grade 1 or 2 in severity. PPES occurred exclusively in patients treated with ripretinib and all events were Grade 1 (13%, 11/85 patients) or Grade 2 (8%, 7/85 patients). Table 20 lists treatment-related TEAEs that occurred in $\geq 10\%$ of patients in the ripretinib group.³⁶

Table 20: Treatment-related TEAEs in $\geq 10\%$ of patients in the ripretinib group compared to placebo – double blind period; safety population, 31 May 2019 DCO (reproduced from CS, Table 23)

Treatment-related TEAE	Ripretinib Grade 1/2 (n=85)	Ripretinib Grade 3/4/5 (n=85)	Placebo Grade 1/2 (n=43)*	Placebo Grade 3/4/5 (n=43)*†
Alopecia	42 (49%)	0	1 (2%)	0
Myalgia	23 (27%)	1 (1%)	4 (9%)	0
Nausea	21 (25%)	1 (1%)	1 (2%)	0
Fatigue	20 (24%)	2 (2%)	6 (14%)	1 (2%)
PPES	18 (21%)	0	0	0
Diarrhoea	17 (20%)	1 (1%)	2 (5%)	1 (2%)
Constipation	13 (15%)	0	3 (7%)	0
Weight loss	13 (15%)	0	3 (7%)	0
Decreased appetite	12 (14%)	1 (1%)	2 (5%)	1 (2%)
Blood bilirubin increased	12 (14%)	0	0	0
Arthralgia	10 (12%)	0	0	0
Muscle spasms	10 (12%)	0	2 (5%)	0

PPES - Palmar-plantar erythrodysesthesia syndrome; TEAE - treatment-emergent adverse event.

* 44 patients were randomised to placebo, but 1 did not receive treatment.

Source: Blay et al, 2020.³⁶

Grade 3/4 treatment-related TEAEs

Grade 3/4 treatment-related TEAEs reported in $>2\%$ of patients in the ripretinib arm included: lipase increase (5%); hypertension (4%); fatigue (2%) and hypophosphataemia (2%). In the placebo arm these were: anaemia (7%); fatigue (2%); diarrhoea (2%); decreased appetite (2%); dehydration (2%); hyperkalaemia (2%); acute kidney injury (2%) and pulmonary oedema (2%).³⁶

Treatment-related SAEs

Treatment-related SAEs were reported in 9% (8/85) of patients receiving ripretinib and 7% (3/43) patients receiving placebo. In the ripretinib group, events included one case each of: anaemia; cardiac failure; death of unknown cause; dyspnoea; fecaloma; gastro-oesophageal reflux disease;

hyperkalaemia; hypophosphataemia; nausea and upper gastrointestinal haemorrhage (some patients may have experienced more than one event). In the placebo group, reported events included one case each of: hyperkalaemia; dehydration; pulmonary oedema; and septic shock (with some patients possibly experiencing multiple events).

3.5.6 AEs of special interest

AEs of special interest (AESI) are shown in Table 21. The CS³ reports that [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Table 21: TEAEs of special interest in double-blind period, safety population (reproduced from CS, Table 22)

Preferred term	Ripretinib (n=85), n (%)	Placebo (n=43)*, n (%)
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

* 44 patients randomised to placebo; one did not receive treatment.
Source: Deciphera Pharmaceuticals. DOF: ripretinib CSR. 2019²

As part of its clarification response in TA881⁴² (question A12), the company sought UK clinical opinion on the clinical significance of these events. The clinician consulted by the company stated that the rates of actinic keratosis should always monitored closely, but with an active and well-tolerated anticancer treatment, dealing with Grade 1-2 keratosis is not a major clinical problem. The clinician also stated that SCC is an important event which needs to be carefully monitored, but that in this population, the benefit of ripretinib is far greater than the disadvantage of SCC, given the low incidence. The company also noted that a dermatopathological review of cutaneous SCC (cuSCC) events in 10 ripretinib-treated GIST patients concluded that patients who developed cuSCC lesions whilst on ripretinib were elderly, with a median age of 76 years. The cuSCC lesions occurred in sun-exposed areas, did not show aggressive histopathological features, and were analogous to their lowest-risk ultraviolet-induced counterparts. Based on this analysis, the company stated that the low-risk cuSCC lesions in patients treated with ripretinib can generally be managed using local interventions without the need for dosing modifications or interruptions.

3.5.7 Pooled AE data

The company pooled together the INVICTUS patient population (n=129) with patients in a Phase 1 study (NCT02571036) with advanced malignancies (n=277 patients).^{34, 36, 39} In the resulting pooled safety population (N=392), the most frequently (>25%) observed adverse reactions in patients who received at least one dose of ripretinib (150mg) were: fatigue (51.0%); alopecia (50.8%); nausea (39.8%); myalgia (37.8%); constipation (37.2%); diarrhoea (32.7%); PPES (29.8%); weight decrease

(26.5%) and vomiting (25.8%). Further details of AEs in the pooled analysis from the August 2020 DCO are presented in Table 22.

Table 22: Adverse reactions in the pooled safety group (N=392) receiving at least one dose of ripretinib (adapted from CS, Table 25)

AE	Any grade AE (>10%)	Grade 3/4 AE (≥2%)	SAEs (≥1%)
Fatigue	51.0%	4.1%	1.5%
Alopecia	50.8%	-	-
Nausea	39.8%	-	1.8%
Myalgia	37.8%	-	-
Constipation	37.2%	-	1.0%
Diarrhoea	37.2%	2.0%	-
PPES	29.8%	-	-
Weight decrease	26.5%	-	-
Vomiting	25.8%	2.6%	2.0%
Lipase increased	23.7%	14.8%	-
Muscle spasms	23.7%	-	-
Arthralgia	21.2%	-	-
Headache	20.7%	-	-
Dyspnoea	20.2%	2.0%	2.3%
Hypertension	19.4%	6.9%	-
Dry skin	17.6%	-	-
Back pain	15.6%	-	-
Cough	15.6%	-	-
Blood bilirubin increased	14.0%	2.0%	1.3%
Oedema peripheral	13.8%	-	-
Hypophosphataemia	12.2%	4.1%	-
Pain in extremity	12.0%	-	-
Pruritis	11.0%	-	-
Seborrhoeic keratosis	11.0%	-	-
Anaemia	-	14.0%	3.8%
Abdominal pain	-	8.2%	-
Muscular weakness	-	-	1.0%

AE - adverse event; SAE - serious adverse event; PPES - palmar-plantar erythrodysesthesia syndrome.
Source: Deciphera Pharmaceuticals, Summary of Product Characteristics (MHRA), 2023²¹

3.5.8 Supportive AE data from Royal Marsden expanded access programme

Table 23 summarises the TEAEs observed in ≥20% patients in the Royal Marsden expanded access programme. The most common TEAEs reported were: fatigue; alopecia; PPES and gastrointestinal and musculoskeletal symptoms.²⁸ The CS³ states that the toxicity outcomes were similar to those observed in the INVICTUS trial,² and no new safety signals were observed.³⁶

In the ripretinib 150mg QD group, 10/45 (22.2%) patients required dose reductions and 2 of 45 (4.4%) patients discontinued ripretinib QD due to persistent toxicities despite adequate dose reductions. After IPDE, 2 of 23 (8.7%) patients required dose reductions. No patient discontinued ripretinib 150mg BID due to toxicity and no treatment-related deaths occurred.²⁸

Table 23: TEAEs reported in at least 20% of patients (in the QD group) in the UK expanded access programme (reproduced from CS, Table 26)

AE	Ripretinib QD Any grade (n=45)	Ripretinib QD Grade 3+ (n=45)	Ripretinib BID Any grade (n=23)	Ripretinib BID Grade 3+ (n=23)
Fatigue	35 (77.8%)	0 (0.0%)	18 (78.3%)	0 (0.0%)
Alopecia	21 (46.7%)	0 (0.0%)	9 (39.1%)	0 (0.0%)
Muscle cramp	20 (44.4%)	0 (0.0%)	4 (17.4%)	0 (0.0%)
PPES	17 (37.8%)	1 (2.2%)	9 (39.1%)	0 (0.0%)
Constipation	17 (37.8%)	1 (2.2%)	8 (34.8%)	0 (0.0%)
Arthralgia/myalgia	15 (33.3%)	1 (2.2%)	6 (26.1%)	0 (0.0%)
Weight loss	14 (31.1%)	0 (0.0%)	13 (56.5%)	0 (0.0%)
Diarrhoea	13 (28.9%)	2 (4.4%)	15 (65.2%)	1 (4.4%)
Anorexia	10 (22.2%)	0 (0.0%)	8 (34.8%)	0 (0.0%)

AE - adverse event; QD - once daily; BID - twice daily; PPES - palmar-plantar erythrodysaesthesia syndrome.

Source: Lim et al, 2024²⁸

3.6 Ongoing studies

The CS³ reports that there are currently no ongoing studies of ripretinib that are relevant to this appraisal.

The EAG is also unaware of any ongoing studies.

3.7 Meta-analysis

The CS³ does not contain any meta-analysis because only one study (the INVICTUS RCT²) was identified in the company's SLR as being relevant to the appraisal. The EAG agrees that meta-analysis is not required.

3.8 Indirect comparison and/or mixed treatment comparison

The CS³ states that no indirect or mixed treatment comparison was conducted because only one study (INVICTUS²) was identified in the SLR as being relevant to the appraisal, and this study included the only comparator of interest (BSC).

3.9 Additional work on clinical effectiveness undertaken by the EAG

No additional work was undertaken by the EAG.

3.10 Conclusions of the clinical effectiveness section

Methods of systematic review: The EAG considers the company's SLR methods to be of a generally good standard. The literature search was subject to some limitations. The electronic search strategy was inadequate for finding all the included studies described in the CS SLR;^{3, 29} however, given the company's supplementary searches, it is unlikely that any relevant studies have been missed.

Clinical evidence: The CS³ presents data from the INVICTUS RCT of ripretinib plus BSC versus placebo plus BSC in 129 patients with advanced GIST who had progressed on, or were intolerant to, (at least) imatinib, sunitinib and regorafenib.² The EAG's clinical advisors considered the patients

enrolled in INVICTUS to be broadly representative of those who would be eligible for treatment in clinical practice in England.

At the May 2019 DCO, median PFS was 6.3 months for ripretinib versus 1.0 months for placebo. The HR for PFS for ripretinib versus BSC was 0.15 (95% CI 0.09 to 0.25, $p < 0.0001$). Median OS was 15.1 months for ripretinib versus 6.6 months for placebo. The HR for OS for ripretinib versus placebo was 0.36 (95% CI 0.21 to 0.62, $p = \text{NR}$). Median OS was 11.6 months in placebo crossover patients, and 1.8 months in placebo non-crossover patients. HRQoL was only reported for both groups during the first cycle (the first 29 days - due to attrition in the placebo arm, patient numbers were low after this point), during which there was improvement in the ripretinib group and worsening in the placebo group based on the EQ-VAS and the EORTC QLQ-C30 (physical and role functioning domains). The most common Grade 3/4 TEAEs with ripretinib (vs. placebo) were: anaemia (11% vs. 14%); abdominal pain (7% vs. 5%); hypertension (7% vs. 0%); increased lipase (5% vs. 0%) and hypophosphataemia (5% vs. 0%). Treatment-related Grade 3/4 TEAEs were reported in [REDACTED] of patients in the ripretinib arm and [REDACTED] of patients in the placebo arm. TEAEs of special interest included SCC of the skin [REDACTED] and actinic keratosis [REDACTED] in the ripretinib and placebo arms, respectively.

In addition, the CS³ included RWE from the Royal Marsden expanded access cohort study.²⁸ However, the EAG notes that 42% of patients included in this study had received only two prior lines of treatment before initiating ripretinib. As this is not consistent with the licensed indication for ripretinib, the relevance of this study to the current appraisal is limited.

As part of the CS,³ the company undertook multiple *post hoc* OS analyses to assess the impact of IPDE in the ripretinib arm. The EAG considers the two-stage approach (provided in response to clarification question B9³⁵) to be the most appropriate among the four analytic approaches explored by the company (Section 3.3.2.1). This analysis suggested that adjusting the effect of dose escalation to reflect no escalation would likely shrink post-progression survival, and consequently, OS. Further details on the application of each method in the company's economic scenario analyses are presented in Section 4.2.5 and critiqued in Section 4.3.5. The company also conducted treatment switching adjustment for OS in the placebo arm; full details are provided in Section 4.2.4.

4. COST EFFECTIVENESS

This chapter presents a summary and critique of the company's health economic analyses of ripretinib for the treatment of patients with advanced GIST after 3 prior therapies. Section 4.1 describes and critiques the company's review of existing economic evaluations. Section 4.2 describes the original version of the company's economic model and summarises its results. Section 4.3 presents the EAG's critical appraisal of the company's economic model. The results of the company's updated (post-clarification) model and the EAG's exploratory analyses are presented separately in Chapter 5.

4.1 Critique of company's review of existing economic analyses

4.1.1 Summary and critique of company's searches

The company performed an initial SLR in July 2020 followed by four update searches in July 2021, March 2022, April 2024 and March 2025. The SLR two-in-one search was undertaken to identify literature for published cost-effectiveness studies (CS Appendix E²⁹) combined with cost and resource use studies (CS Appendix G) in patients who have advanced, unresectable, or metastatic patients with 4L+ GIST.

The company searched all relevant electronic bibliographic databases in March 2025 (CS Appendix E,⁵⁶ Table 14) via the Ovid host platform, notably Medline, Embase, HTA, NHS EED and Econlit, as well as CDSR; CENTRAL, the ACP Journal Club, DARE, Cochrane Clinical Answers and the Cochrane Methodology Register.

As with the clinical effectiveness SLR searches, three conference abstract websites were searched for the last five years (2021-2025): ASCO, ESMO, and ASCO Gastrointestinal Cancers Symposium. The company searched clinicaltrials.gov registry for ongoing or completed or unpublished trials. Four HTA agency websites were searched: NICE, SMC, PBAC and CDA-AMC.

The company combined the search for the population (disease GIST) with the various economic outcomes, health care and resource use filters. The Cochrane Handbook refers to additional terms that could have been included in the burden of illness search filter (Aluko *et al.*,⁵⁷ 2023). Other than the limitation of restricting the search to English language studies, there were no issues or errors in the search and the EAG considers that the search is comprehensive.

For the review of HRQoL studies, an initial search was carried out in July 2020 followed by four updates in July 2021, March 2022, April 2024 and March 2025. The company searched the same sources as in the cost-effectiveness and health costs and resource use searches, i.e., electronic database and grey literature searches. The company combined the search for the population (GIST AND "metastatic/advanced/unresectable" AND relapsed/refractory/resistant) with an HRQoL outcomes

search filter. There were no errors in the search and the EAG considers that the search is comprehensive and relevant studies are unlikely to have been missed.

4.1.2 *Summary and critique of company's review of existing economic evaluations*

The inclusion criteria for the company's review of published economic evaluations are reported in Table 9 of CS Appendix E.²⁹ Studies were eligible for inclusion in the review if the population included in the analysis related to people with advanced, metastatic or unresectable GIST at any line of treatment. The inclusion criteria also specified that studies must be economic evaluations, budget impact analyses, or burden of illness studies, or must report measures of costs and/or health care resource use. No restrictions were applied to the interventions or comparators assessed within the studies. Editorials, reviews, comments, and letters were excluded, as were studies not published in the English language and studies published prior to 2000. Extracted data from the identified records were provided in a separate SLR Excel workbook provided as part of the CS references.

Across the original and update searches, a total of 36 unique studies were included in the review. Twenty-four of the identified studies were cost-effectiveness/cost-utility analyses, three were budget impact analyses and nine were health care resource use studies. The company's quality assessment of the included economic evaluations using the Drummond checklist⁵⁸ is provided in the SLR Excel workbook. The results of this quality assessment are presented in tabular form only; a narrative summary of the quality assessment is not provided in either the CS or the CS appendices.^{3, 29} Table 12 of CS Appendix E summarises all included economic evaluation studies regardless of geographical setting; Table 27 of the main CS summarises the subset of UK economic evaluation studies.

The economic analyses included in the company's broader review used a variety of modelling approaches, including state transition, partitioned survival and simulation models. Treatments evaluated included: surgical resection; imatinib; sunitinib; regorafenib; ripretinib; pazopanib and standard care (including no treatment, BSC, palliative care and placebo). Studies were conducted in various settings including: Brazil; Canada; China; England; Germany; the Netherlands; France; Mexico; Singapore; Spain; Turkey; the UK and the US. None of the UK-based cost-effectiveness studies included ripretinib as an intervention.

One non-UK study (Liao *et al.*⁵⁹) evaluated ripretinib versus placebo as a 4L+ treatment for advanced GIST. Liao *et al.* reports the methods and results of a health economic model in which parametric survival models were fitted to replicated IPD from the INVICTUS trial.² The authors state that the model uses a Markov approach; however, the survival model parameters reported in the paper relate to the end points of PFS and OS, which indicates that the model is a partitioned survival analysis. The analysis did not include statistical adjustment of the OS data to account for confounding resulting from

placebo group patients switching onto ripretinib; instead, the costs of post-progression ripretinib (after switching) were included in the total costs for the BSC group. In addition, the text indicates that the costs of continued post-progression ripretinib in INVICTUS were excluded from the total costs for the intervention group. Health state utility values were taken from analyses of EQ-5D-3L data collected in the GRID trial (regorafenib versus placebo in patients with metastatic/unresectable GIST who have progressed on or were intolerant to imatinib and who have progressed on sunitinib; PF utility = 0.767; PD utility = 0.647).⁶⁰ The authors report an incremental cost-effectiveness ratio (ICER) for ripretinib versus placebo of US \$244,010 per quality-adjusted life year (QALY) gained. The EAG notes that the study by Liao *et al.* is limited due the absence of any statistical adjustment to account for confounding of the OS data due to placebo treatment switching in INVICTUS and the exclusion of post-progression ripretinib costs from the intervention group of the model.

4.2 Summary of the company's original submitted economic analysis

4.2.1 Scope of the company's economic analyses

As part of their submission to NICE,³ the company submitted an executable health economic model programmed in Microsoft Excel. The scope of the company's economic analysis is summarised in Table 24.

Table 24: Scope of the company's economic analysis

Population	Patients with advanced GIST after 3 or more therapies, including imatinib
Time horizon	40 years (lifetime)
Intervention	Ripretinib 150mg QD (administered orally)
Comparator	BSC
Type of economic analysis	Cost-utility analysis
Outcome	Incremental cost per QALY gained
Perspective	NHS and PSS
Discount rate	3.5% per annum
Price year	2023/2024 (except for drug costs which reflect current prices)

GIST - gastrointestinal stromal tumour; mg - milligram; QD - once daily; QALY - quality-adjusted life year; NHS - National Health Service; PSS - Personal Social Services

The company's economic model assesses the cost-effectiveness of ripretinib (plus BSC) versus BSC alone for the treatment of patients with advanced GIST after at least three therapies, including imatinib. Cost-effectiveness is assessed in terms of the incremental cost per QALY gained from the perspective of the NHS and Personal Social Services (PSS) over a 40-year (lifetime) horizon. Unit costs are valued at 2023/2024 prices, except for drug acquisition costs which are valued at current prices. Health outcomes and costs are discounted at a rate of 3.5% per annum.

Population

The company's economic analysis is intended to reflect the population of patients with advanced GIST who have received three or more prior therapies, including imatinib (i.e., the company intends to position ripretinib as a 4L+ therapy). Patient characteristics are based on the population enrolled in the INVICTUS trial.² At model entry, patients are assumed to be 60.1 years of age and 43.41% of patients are assumed to be female.

As noted in Section 3.2.1, approximately 37% of patients in INVICTUS² had already received at least four prior lines of treatment at study entry (see Table 7). The EAG's clinical advisors commented that the number of prior therapies received is likely to be a prognostic factor.

Intervention

The intervention included in the company's economic analyses is ripretinib, administered orally at a dose of 150mg (taken as 3 x 50mg tablets) daily. This is in line with the final NICE scope²⁰ and the MHRA marketing authorisation for ripretinib.⁴⁹ The SmPC for ripretinib (page 2) states that "*treatment with QINLOCK should continue as long as benefit is observed or until unacceptable toxicity.*" In contrast to the previous model used to inform TA881,¹ the model for the current appraisal includes the continued use of ripretinib treatment after disease progression (i.e., a progression-based stopping rule is no longer applied). As noted in Section 3.2.1, patients who experienced disease progression in INVICTUS² were allowed to continue on the current dose of ripretinib 150mg QD or dose-escalate to ripretinib 150mg BID; the higher dose of ripretinib is not in line with the marketing authorisation for ripretinib. The company's base case model does not include any statistical adjustment of the OS data from INVICTUS² to account for the effects of ripretinib 150mg BID dosing and the post-progression ripretinib drug costs are based on the QD dosing regimen. This issue is discussed further in Section 4.3.5. The model assumes that patients do not receive any further active anticancer treatment after discontinuing ripretinib (i.e., they receive BSC alone).

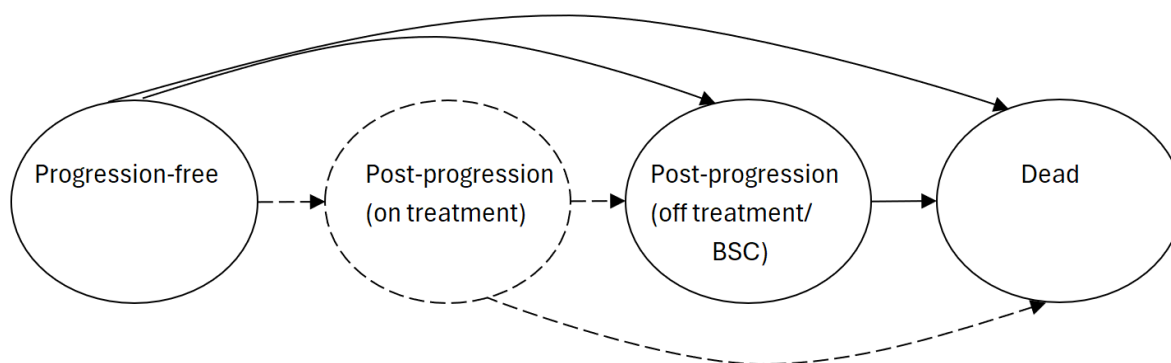
Comparator

The company's base case analysis includes a single comparator: BSC (no active therapy). The economic model includes costs associated with: pain management (analgesics); computed tomography (CT) and magnetic resonance imaging (MRI) scans; full blood counts (FBCs) and liver function tests (LFTs); outpatient appointments; palliative resection; palliative radiotherapy (RT); the management of AEs and end-of-life care (see Section 4.2.4).

4.2.2 Model structure and logic

The company's economic model adopts a partitioned survival approach, including four health states: (i) progression-free; (ii) progressed disease (on treatment with ripretinib); (iii) progressed disease (off treatment with ripretinib/BSC), and (iv) dead (see Figure 17).

Figure 17: Company's model structure (drawn by the EAG)



BSC - best supportive care

Dashed arrows and ellipses indicate parts of the model which are applicable to the ripretinib treatment group only

The model logic operates as follows. Patients enter the model in the progression-free state and receive treatment with either ripretinib (plus BSC) or BSC alone. At any time t , health state occupancy is determined by the cumulative probabilities of OS, PFS and TTD, whereby:

- The probability of being alive and progression-free is given by the cumulative probability of PFS;
- The probability of being alive following disease progression is calculated as the cumulative probability of OS minus the cumulative probability of PFS;
- The probability of being on treatment following disease progression is calculated as the cumulative probability of having progressed and discontinued treatment minus the cumulative probability of PFS (this applies to the ripretinib group only);
- The probability of being dead is calculated as one minus the cumulative probability of OS.

The company's model includes half-cycle correction. Patients in the ripretinib group are assumed to receive treatment during the entire PFS period and during part of the post-progression survival period. No further active anticancer treatments are assumed to be given after disease progression in the ripretinib group, or to any patient in either of the alive health states in the BSC group.

The cumulative probabilities of OS and PFS for patients receiving ripretinib and BSC are modelled using parametric survival distributions fitted to time-to-event data from the INVICTUS trial.² The model applies a structural constraint whereby if the per-cycle risk of death from the parametric survival model is lower than that for the age- and sex-matched general population (based on Office for National Statistics [ONS] life tables⁶¹) in any given cycle, the general population mortality risk is used, otherwise

the unadjusted OS probability is used. This aspect of the model is subject to an error (see Section 5.3.5, critical appraisal point 1). In addition, the model includes a constraint which ensures that the PFS function cannot be higher than the adjusted OS function at any time point. No other structural constraints are included in the model.

HRQoL is assumed to be determined by the presence/absence of disease progression and whether patients receive ripretinib treatment after progression. The utility values applied in the progression-free (PF) and progressed disease (PD) states are based on EQ-5D-5L data (mapped to the 3L version) collected in INVICTUS.^{2,3} Utility values are adjusted for increasing age. The model also includes short-term QALY losses associated with Grade 3/4 TEAEs occurring in $\geq 5\%$ of either group in the double-blind period of INVICTUS, based on disutility values reported in other literature.^{62, 63} Based on the description in the CS, all TEAEs are assumed to have a duration of one model cycle (approximately 28 days), although this part of the model is also subject to an error (see Section 4.3.5, critical appraisal point 1).

The model includes costs associated with: (i) drug acquisition (ripretinib and BSC pain management drugs); (ii) health state management (scans, tests and outpatient visits); (iii) pre-treatment resource use (scans and tests); (iv) palliative treatments; (v) the management of AEs and (vi) end-of-life care costs. Drug acquisition costs for ripretinib are modelled as a function of the TTD distribution, relative dose intensity (RDI) and unit costs. BSC pain management costs and health state costs are applied in each model cycle. Palliative treatment costs are applied once in the first model cycle and once again at the point of disease progression. Other costs are applied once only at specific time points - either at model entry, on disease progression or at the point of death.

The incremental health gains, costs and cost-effectiveness for ripretinib versus BSC are estimated over a 40-year time horizon using a 28.10-day cycle duration (1/13th of a year). No economic subgroup analyses are presented in the CS.³

4.2.3 Key assumptions employed in the company's base case model

The company's base case model employs the following key assumptions:

- The modelled population is 60.10 years of age at model entry.²
- The model assumes that patients receive ripretinib prior to disease progression and treatment may be continued beyond progression. Patients do not go on to receive further active treatments after discontinuing ripretinib or after progression on BSC.
- BSC is the sole comparator for ripretinib.

- TTD for ripretinib is modelled using an exponential distribution. PFS is modelled using independently fitted log-normal distributions in both treatment groups. OS is modelled using independently fitted log-logistic distributions in both treatment groups.
- The model includes a structural constraint which should prevent the mortality risk for people with advanced GIST from being lower than that for the age- and sex-matched general population (although this has been implemented incorrectly; see Section 4.3.5). The model also assumes that the cumulative probability of PFS cannot be greater than the cumulative probability of OS at any time point. No other constraints are included. Given the use of a partitioned survival approach, the risks of progression and death are structurally unrelated.
- Dose escalation to ripretinib 150mg BID in patients with disease progression in INVICTUS² is assumed not to have impacted on OS estimates relative to QD dosing. All post-progression ripretinib costs are based on the ripretinib 150mg QD dose. Taken together, the model assumes that the outcomes observed in INVICTUS (including the effects of post-progression ripretinib 150mg BID dosing in some patients) can be achieved by using the 150mg QD dose in all patients.
- HRQoL is determined by the presence/absence of disease progression and whether patients receive ripretinib after disease progression. The same utility values for the PF and PD (off treatment) states are applied in each treatment group. The utility value applied to patients who remain on ripretinib treatment after progression lies between the values for the PF and PD (off treatment) states. Utility values are adjusted for increasing age.
- AEs result in QALY losses and additional costs. The CS³ indicates that AEs are assumed to be resolved within the first 28-day model cycle (although the model is subject to an error whereby AE-related QALY losses are applied in all cycles).
- Prior to disease progression, pre-treatment and disease management costs are assumed to be higher for patients receiving ripretinib compared with those receiving BSC alone. The same costs per cycle/event for pain management, the management of progressed disease after ripretinib discontinuation, palliative treatments and end-of-life care are applied to the ripretinib and BSC groups.

4.2.4 Evidence used to inform the company's model parameters

Table 25 summarises the evidence sources used to inform the base case model parameters. The derivation of the model parameter values is discussed in detail in the subsequent sections.

Table 25: Summary of evidence used to inform the company's base case analyses

Parameter / group	Ripretinib	BSC
Patient characteristics (age and sex)	INVICTUS ²	
TTD	Exponential distribution fitted to composite end point of PFS+TTD (QD or BID dosing) over the double-blind and open-label periods of INVICTUS ² (see clarification response, ³⁵ question B2 for further details)	N/a
PFS	Log-normal model fitted to ripretinib group PFS data from INVICTUS ²	Log-normal model fitted to placebo group PFS data from INVICTUS ²
OS	Log-logistic model fitted to ripretinib group OS data from INVICTUS. ² No adjustment is applied to the data to account for the effects of ripretinib 150mg BID on OS.	Log-logistic model fitted to BSC group OS data from INVICTUS, ² adjusted for placebo group treatment switching using the simple 2-stage method with re-censoring.
General population mortality	ONS life tables for the UK ⁶¹	
Health state utility values	EQ-5D-5L data collected in INVICTUS ² mapped to the 3L version using Van Hout <i>et al.</i> ⁶⁴	
TEAE frequencies	Grade 3/4 TEAEs arising in $\geq 5\%$ of patients in either group in INVICTUS ²	
TEAEs disutilities	Harrow <i>et al.</i> , ⁶² Doyle <i>et al.</i> ⁶³ and assumptions	
TEAE duration	Assumption (intended duration = 28 days)	
Drug acquisition costs	List price taken from the BNF. ²⁶ PAS discount for ripretinib provided by the company. ³ RDI estimates taken from INVICTUS. ²	N/a
BSC pain management costs	Drug usage was based on a physician survey undertaken to inform NICE TA488 (regorafenib for GIST), ⁴⁵ with additional information on dosing taken from NICE TA730 (avapritinib for GIST). ⁶⁵ Drug acquisition costs were taken from the BNF. ²⁶ The commonly prescribed dosage form of each product was determined using Prescription Cost Analysis data. ⁶⁶	
Health state costs	Resource use was based on a physician survey undertaken to inform TA488. ⁴⁵ Unit costs were taken from the NHS Cost Collection 2023/24. ⁶⁷	
Pre-treatment costs		
Palliative treatment costs		
TEAE management costs	NHS Cost Collection 2023/24. ⁶⁷	
End-of-life care costs	The cost of death by location was taken from TA488 ⁴⁵ (based on Abel <i>et al.</i> ⁶⁸). Costs were uplifted to current prices using HCHS/NHSCII indices. ⁶⁹	

BSC - best supportive care; PFS - progression-free survival; OS - overall survival; TTD - time to treatment discontinuation; ONS - Office for National Statistics; TEAE - treatment-emergent adverse event; EQ-5D-5L - Euroqol 5-Dimensions 5-Level; 3L - 3-level; QD - once daily; BID - twice daily; N/a - not applicable; TA - Technology Appraisal; BNF - British National Formulary; HCHS - Hospital and Community Health Services; NHSCII - NHS Cost Inflation Index

4.2.4.1 Time-to-event parameters

Statistical adjustment of OS data to account for treatment switching in the placebo group and intra-patient dose escalation (IPDE) dosing in the ripretinib group

As discussed in Section 3.2.1, within both groups of the INVICTUS trial,² a change in treatment could occur following disease progression. Patients who were randomised to receive placebo had the option to commence treatment with ripretinib 150mg QD after progression and could increase their dose to 150mg BID on further progression. Patients who were randomised to receive ripretinib (plus BSC) could remain on treatment at their current dose (150mg QD), increase their dose (to 150mg BID) or discontinue ripretinib. The decision to remain on ripretinib (at either the current or increased dose) was informed by the investigator's view of whether the patient was obtaining benefit from ripretinib, if dose escalation could be tolerated and whether or not they had access to additional therapies.⁴ An overview of the treatment changes that occurred during the trial is provided in Section 3.2.2. The company's base case economic model includes statistical adjustment for treatment switching onto ripretinib in the BSC group but does not include adjustment to account for IPDE to the 150mg BID dose in the ripretinib group. Six alternative approaches to adjusting for IPDE are considered in the company's scenario analyses (see Table 41). Additional IPDE adjustment analyses were provided as part of the company's clarification response.³⁵ The subsequent sections describe the methods and results of the company's adjustment of OS to account for treatment switching in the placebo group and IPDE to ripretinib 150mg BID in the intervention group of INVICTUS.

Adjustment of OS data to account for treatment switching onto ripretinib in the placebo group (included in the base case model)

The company's adjustment of the placebo group OS data to account for placebo group patients switching onto ripretinib remains unchanged from the analysis presented in TA881.¹ At the 15th January 2021 DCO of INVICTUS,² 30 of the 44 (68%) patients in the placebo arm had crossed over to receive ripretinib following disease progression, with the majority of switches occurring less than four weeks (one model cycle) after disease progression (mean [REDACTED] weeks).⁴ NICE DSU TSD 16⁴⁸ details three main approaches which may be considered to adjust estimates of OS for treatment switching: (i) IPCW; (ii) RPSFTM; and (iii) two-stage estimation methods. All three approaches are discussed in the CS,³ although IPCW was not considered for formal analysis by the company due to the small sample size and the large proportion of patients switching. The other two methods – the RPSFTM and two-stage estimation approaches – were both explored. An RPSFTM was implemented using the *rpsftm* package in R. This approach relies on the 'common treatment effect' assumption, which in this case, assumes that the delay in receiving ripretinib observed in the subset of placebo group patients who switched to receive ripretinib in INVICTUS² (compared to the ripretinib arm) has not influenced OS outcomes. A plot of counterfactual event times provided in Figure 26 of the CS was used to assess this assumption; this plot suggests that the common treatment effect assumption is likely to be violated.

The two-stage approach (with re-censoring) was used in the company's base case economic model. This approach relies on there being an appropriate secondary baseline at the point of treatment switching, with no unmeasured confounding at this point. Time of disease progression was taken as the secondary baseline, with measurements of covariates that were closest to this time point being used in the analyses. Two models were considered for the two-stage approach: a 'simple' model in which the only covariate was time to progression, and a 'complex' model which also included age, HRQoL (measure not stated), and ECOG PS. Median switching-adjusted OS for the placebo arm was [REDACTED] and [REDACTED] weeks for the simple and complex models, respectively. The company used the simple two-stage model in its base case analysis on the basis that time to progression was the only statistically significant variable in the complex model and retaining additional variables would add to uncertainty.

The CS³ reports the results of several scenario analyses relating to the statistical adjustment of OS data to account for treatment switching from placebo to ripretinib. These included: unadjusted OS; the simple two-stage approach; the complex two-stage approach and the RPSFTM approach. Each adjustment approach was applied separately with and without re-censoring. In addition, two further RPSFTM analyses were conducted which relax the common treatment effect assumption (assuming $k_i=0.50$). The results of these scenario analyses are reproduced in Table 41 (Scenarios S19 to S26). Estimates of cost-effectiveness were not particularly sensitive to the adjustment method chosen, with the ICER for ripretinib versus BSC ranging from £27,470 to £31,104 per QALY gained (including QALY weighting). The company's deterministic base case ICER is near the middle of this range (£28,836 per QALY gained). As expected, the ICER for ripretinib versus BSC was substantially higher when switching adjustment was excluded from the analysis (Scenario S19: ICER = £61,731 per QALY gained).

In TA881,¹ the ERG requested further information from the company regarding the approach used to implement the two-stage estimation method. The analyses provided used a log-normal model to derive the counterfactual OS as if no crossover occurred in the placebo group; this model had the lowest Akaike Information Criterion (AIC) value of the five parametric survival models considered (the exponential, log-normal, log-logistic, Weibull, and generalised gamma distributions). Estimates of switching-adjusted median OS for placebo from the exponential model lacked face validity, whilst estimates from other models showed little variation: compared with the log-normal model estimate of [REDACTED] weeks, estimates for the other models ranged from [REDACTED] to [REDACTED] weeks. The impact of these alternative models on the cost-effectiveness of ripretinib was not explored, but this is not expected to be a key driver.⁴

Seven patients in the placebo group had censored times of disease progression. When performing the statistical adjustment of OS data to account for treatment switching in the placebo group, these patients were assumed to have an observed progression time equal to their censored progression time. The company stated that of these seven patients, three had crossed over to ripretinib treatment.⁴

Adjustment of OS data for IPDE in the ripretinib group (included in the company's scenario analyses only)

The adjustment of OS data in the ripretinib group to account for IPDE to post-progression ripretinib 150mg BID dosing was not a relevant consideration in TA881¹ because the company's economic model included a stopping rule at the point of disease progression. The company's model for the current appraisal allows for continued treatment with ripretinib following disease progression. As 150mg BID dosing represents an off-label use of ripretinib,²¹ the company applied a variety of methods to adjust the OS data to attempt to estimate the counterfactual OS under ripretinib 150mg QD dosing - though only one approach (i.e., two-stage adjustment) is aligned with that intent. These methods were only applied in the company's scenario analyses; the base case analysis does not include any adjustment of the OS data in the ripretinib group.

Approaches for IPDE adjustment undertaken by the company are summarised in the clinical section of this EAG report (Section 3.3.2.1, Table 11). Of the four approaches listed in CS³ Section 2.6.2 and CS Section 3.3.2, Approach 1 (Open-label BID vs QD OS analysis) included three variations (Approach 1(a) to 1(c) in Table 11). Approach 1(a) and 1(b) were presented in CS Figures 9 and 10, and Approach 1(c) was presented in response to clarification question B3.³⁵ These were descriptive analyses of OS in mutually exclusive subgroups within the ripretinib arm (i.e., with or without dose escalation), exploring the impact of IPDE. The company did not include these in scenario analyses, which the EAG considers reasonable given the key biases outlined in Section 3.3.2.1.

The company's scenario analyses included two variations of each of the remaining three approaches (as described in Table 11):

- Approach 2: Censored BID-dosing analysis
- Approach 3: Time-varying Cox proportional hazards model
- Approach 4: Two-stage adjustment.

Among the three approaches, only the two-stage estimation is recommended in NICE TSD24⁷⁰ for adjusting (i.e., removing) the effects of subsequent treatments that differ (ripretinib 150mg BID) from those in the original randomised arm (ripretinib 150mg QD). IPCW would be an appropriate alternative; however, the company did not apply this method due to the small sample size.

The EAG provides a detailed summary and critique of the three approaches that informed the company's scenario analyses in the subsequent sections. Please refer to Table 11 for the corresponding method numbers.

Approach 2: Censored BID-dosing analysis

Approach 2(a) compared OS in the ripretinib arm with and without censoring patients at the point at which they escalated to BID dosing (CS,³ Figure 11). The censored analysis showed slightly improved OS, which suggests that excluding BID dosing leads to better outcomes. This contradicts the views of the clinicians who attended the company's 2024 advisory board meeting⁴⁰ and the EAG's clinical advisors. Nevertheless, since patients were not randomised to receive BID, this analysis is likely to be biased due to informative censoring and does not reflect a fair comparison. The company did not use this analysis for scenario analysis.

In Approach 2(b), the company compared OS between two non-mutually exclusive subgroups: (i) patients with progressed disease who escalated to BID dosing combined with those whose disease did not progress versus (ii) patients with progressed disease who did not escalate to BID dosing combined with those whose disease did not progress (see Table 11 and CS, Figure 12). The first group showed OS similar to the unadjusted OS, while the second group had worse OS. These analyses aimed to "isolate" the effect of post-progression BID and QD dosing, respectively. However, as patients were not randomised to dose escalation, selecting subgroups based on post-randomisation characteristics introduces selection bias. In particular, attrition bias is apparent: the proportion of non-progressors in each of these analyses would not reflect the natural rate of progression and non-progression in the overall population. Consequently, these comparisons do not allow for reliable inferences about the causal effect of dose escalation.

Six parametric models (exponential, generalised gamma, Gompertz, log-logistic, log-normal, and Weibull) were fitted to the adjusted OS for survival extrapolation, with the AIC and Bayesian information Criterion (BIC) statistics indicating the exponential model as the best fit for the "plus BID progressors" subgroup and the log-normal model for the "plus QD progressors" subgroup. However, the company selected the log-logistic model for both scenario analyses, referred to as "Open-label BID vs QD OS (non-progressors + IPDE progressors)" (Scenario S34 in Table 41) and "Open-label BID vs QD OS (non-progressors + QD progressors)" (Scenario S35 in Table 41). These scenario analyses resulted in slightly higher ICERs (£31,371 and £30,142 per QALY gained, respectively) than the company's base case.

The company did not provide further justification for selecting log-logistic models for survival extrapolation in these two IPDE-adjusted OS scenario analyses (Approach 2(b)(i) and 2(b)(i) in Table 11). This choice reflects the company's use of log-logistic models as in its preferred base case with unadjusted ripretinib OS, and because the log-logistic models showed the lowest combined AIC values for the IPDE-adjusted ripretinib OS (CS, Table 34) and placebo OS (with two-stage adjustment) (CS, Table 33).

Approach 3: Time-varying Cox proportional hazards model

The company conducted three time-varying Cox proportional hazards models for dose escalation adjustment, each with a different set of time-varying covariates (Approach 3(a)-3(c) in Table 11; corresponding HRs are reported in CS,³ Table 35):

- Model 1 included only IPDE as a covariate
- Model 2 included IPDE, progression status, ECOG score, EQ-5D VAS, lesion diameter (change from baseline)
- Model 3 included all variables in Model 2, plus baseline lesion diameter sum, age, sex, race, region, baseline BMI, hepatic impairment, number of prior therapies, baseline creatinine clearance, and baseline renal impairment.

Each model produced a HR estimating the effect of IPDE on OS, with all HRs > 1.0 and 95% CIs crossing 1.0, indicating a non-statistically significant association with reduced survival. The treatment-only model (Model 1, HR=1.58; 95% CI: 0.85 to 2.95; Approach 3(a) in Table 11 and Scenario S32 in Table 41) and the full model (Model 3, HR=1.37; 95% CI: 0.66 to 2.84; Approach 3(c) in Table 11 and Scenario S33 in Table 41) were used in scenario analyses. For each analysis, a weighted average HR was applied to the base case OS curve in the ripretinib arm, with weights based on the proportion of patients in the on-treatment PD state, determined by the selected OS and TTD curves. The adjustment was implemented as:

$$\text{Adjusted OS} = \text{OS}^{(1 + \text{Proportion\_PDO} \times (\text{HR} - 1))}.$$

These analyses resulted in slightly higher ICERs compared with the company's base case, at £29,347 and £29,162, respectively. In response to clarification question B7,³⁵ the company corrected an error in these analyses whereby 13 patients were assigned a death event in multiple periods. The updated analysis yielded a revised HR of 1.50 (95% CI: 0.70 to 3.22; $p=0.300$). However, the company did not specify which time-varying Cox model was corrected, and no updated ICERs were provided following the correction.

The EAG highlights two key concerns with the time-varying Cox model approach. First, the HR was estimated for the full OS dataset but is applied only to a subset of patients with progressed disease who remain on treatment – this leads to a mismatch between estimation and application. Second, because dose escalation was not randomised, simply including time-varying covariates (i.e., time-varying treatment exposure and time-varying confounders) in a Cox model, without causal inference methods, such as a marginal structural model, cannot address time-varying confounding and limits the ability to interpret the causal effect of IPDE on OS. This likely explains the counterintuitive HR that suggests that IPDE to ripretinib 150mg BID is harmful versus continued QD treatment, which contradicts clinicians' expectations that dose escalation would be given to patients who are likely to benefit and can tolerate it.

Approach 4: Two-stage adjustment

In the two-stage estimation approach, the company used methods similar to those for crossover adjustment in the placebo arm. This involved estimating a time ratio to shorten or extend post-progression survival (the period during which ripretinib BID was received), aiming to derive the counterfactual OS had patients continued ripretinib 150mg QD instead of escalating to BID dosing after progression. This method requires establishing a suitable secondary baseline at the point of treatment-switching (i.e., initiation of subsequent treatment) and assumes no unmeasured confounding at this point. The company defined disease progression as the secondary baseline, using covariate measurements closest to this event.

A simple two-stage model (without g-estimation) is valid only if there is no time-varying confounding between progression and initiation of subsequent treatment, and if subsequent treatment consistently follows progression (i.e., occurs on the same date or close to it). Although the company did not provide evidence on the interval between progression and initiation of subsequent treatment, this gap is likely to be small, given the advanced stage of disease in this patient population. Therefore, the EAG considers the simple two-stage approach without g-estimation to be reasonable.

In the first stage, two sets of models were considered for the two-stage approach to generate time ratios (Approach 4(a) and 4(b) in Table 11): the ‘simple’ model included only time to progression as a covariate, while the ‘complex model’ additionally incorporated age, EQ-5D VAS score at progression, and ECOG PS at progression. Each model was fitted using a range of parametric distributions, including the exponential, Weibull, log-normal, log-logistic and generalised gamma distributions. The Gompertz distribution was also added in response to clarification question B9.³⁵

In all cases, time ratios were greater than 1.0 (with some 95% CIs crossing 1.0), indicating prolonged survival for patients who received dose escalation dosing compared with those who remained on QD dosing (CS Table 36; response to clarification question B9³⁵). For the scenario analysis, the company selected the log-normal distribution for the simple model (time ratio = 3.45; 95% CI: 1.56 to 7.60; Scenario S30 in Table 41) and the generalised gamma distribution for the complex model (time ratio = 2.72; 95% CI: 1.57 to 4.74; Scenario S31 in Table 41), as these had the lowest AIC values within their respective model types (CS, Table 36).

The second stage involved applying the time ratio to estimate counterfactual OS, as if patients had continued QD dosing without dose escalation. The company incorporated these time ratios through a ‘weighted average hazard adjustment’ to the OS base case parametric model for the ripretinib arm. Time ratios were treated as equivalent to inverse HRs and weighted by the proportion of patients in the on-treatment PD partition. The adjustment was implemented in the economic model using the following formula:

$$\text{Adjusted OS} = \text{OS}^{(1 + \text{Proportion\_PDOnRip} \times ([1 / \text{SurvivalTimeRatio}] - 1))}$$

The EAG notes several concerns regarding this approach. First, time ratios should not be used to derive HRs, as these are conceptually distinct measures. Time ratios are calculated based on accelerated failure time (AFT) models, whereas HRs arise from proportional hazards (PH) models. Only the exponential and Weibull distributions can be directly expressed under both modelling frameworks. Even in those cases, the transformation $HR = 1 / \text{time ratio}$ is only valid for the exponential distribution. Second, the company inappropriately applied a uniform time ratio adjustment to all patients who had progressed at each time point in the model, rather than restricting it to those who actually underwent dose escalation. This application is inconsistent with the derivation of the time ratio, which was based on patients who had progressed and remained on treatment at each time point.

The approach to implementation in the economic analysis described above was further simplified by relying on a summary percentage rather than IPD, which undermines the validity of the analysis. Overall, the EAG recommended in clarification question B9³⁵ that the company instead conduct the two-stage adjustment using an approach similar to that employed for crossover adjustment in the placebo arm and to use the resulting counterfactual OS for survival extrapolation.

In response to clarification question B9,³⁵ the company provided a comprehensive update, which the EAG considers to be reasonable. Specifically, counterfactual OS was derived using time ratios from each of the six distributions, following an approach similar to that used for crossover adjustment in the placebo arm. This was done with and without re-censoring, resulting in 12 counterfactual OS scenarios. Parametric survival models (the exponential, Weibull, Gompertz, log-normal, log-logistic, and generalised gamma distributions) were then fitted to each counterfactual OS dataset for extrapolation (i.e., $12 \times 2 \times 6 = 144$ scenarios).

The company did not provide updated ICERs for each of these scenarios but included functionality to apply each of these distributions and adjustments within their updated economic model. Among all scenarios, the complex model using the generalised gamma distribution to derive the time ratio had the lowest AIC, indicating the best statistical fit for estimating counterfactual OS, as if all patients had continued on ripretinib QD dosing without dose escalation.

In summary, for the IPDE adjustment scenario analyses, the EAG considers the company's updated two-stage adjustment approach, as outlined in their response to clarification question B9,³⁵ to be reasonable and in line with TSDs 16 and 24.^{48, 70} In contrast, the EAG considers all other approaches applied by the company to be unsuitable for informing decision-making, as they fail to support a causal interpretation of the IPDE effect due to time-varying confounding and selection bias not being appropriately addressed, and/or because they suffer from questionable implementation within the company's economic model.

Summary of parametric survival model fitting process and model selection

The company fitted a series of standard parametric survival models to the time-to-event data on TTD+PFS (as a composite end point), PFS and OS (adjusted for treatment switching onto ripretinib in placebo group) from INVICTUS.² The DCO for TTD, PFS and OS was the 15th January 2021;³ this is the same DCO applied in TA881.¹ The company's base case model for the current appraisal does not include any adjustment of OS for ripretinib IPDE or the costs of ripretinib 150mg BID dosing following progression in the intervention group, although these factors are considered in the company's scenario analyses (see Table 41).

The same general survival modelling approach was applied to both the PFS data and the switching-adjusted OS data. For each end point, the company assessed the PH assumption to determine whether it is reasonable to fit models which include a treatment-indicating covariate (an HR). This was done by examining log-cumulative hazard plots, plotting Schoenfeld residuals and performing Schoenfeld global tests. There was evidence to suggest that the PH assumption was violated for PFS, but that it may be a reasonable assumption for OS. Quantile-quantile (Q-Q) plots which can be used to assess the appropriateness of using jointly fitted AFT models are not presented in the CS.³ The company elected not to use jointly fitted models and instead fitted models independently to the data for each treatment group. These considerations were not necessary for TTD as this end point is only relevant to the ripretinib group. The company fitted six standard parametric survival models to the PFS and OS data, including the exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma distributions. For TTD, the company fitted the same six models as well as the gamma and generalised F models, although the latter two distributions are not included in the executable economic model. More flexible parametric survival distributions, such as restricted cubic spline (RCS) models, were not considered for TTD, PFS or OS.

The CS³ indicates that the company's model selection process included consideration of: relative goodness-of-fit statistics using the AIC and BIC, visual inspection of the fitted models and plausibility based on expert opinion obtained from clinicians consulted during three advisory board meetings held by the company in 2022, 2024 and 2025.^{27, 40, 41} The CS also mentions that the same parametric survival distributions were selected for both treatment groups. The CS does not present empirical or modelled hazard plots for OS or PFS; however, these were provided as part of the company's response to clarification questions in TA881.¹ A plot showing the hazard functions for the models fitted to the TTD+PFS data is presented in CS Appendix J;²⁹ an updated plot was provided as part of the company's clarification response.³⁵ The CS indicates that the expected shape of the hazard functions for OS and TTD was discussed with clinical experts; it is unclear from the CS whether the hazard plots were used to inform model selection for PFS.

TTD+PFS (composite end point)

AIC and BIC statistics for the fitted TTD+PFS models are summarised in Table 26. The smoothed empirical and modelled hazard functions for TTD+PFS are shown in Figure 18. Comparisons of the observed Kaplan-Meier survival functions and the parametric survival model predictions for ripretinib TTD+PFS are shown in Figure 19.

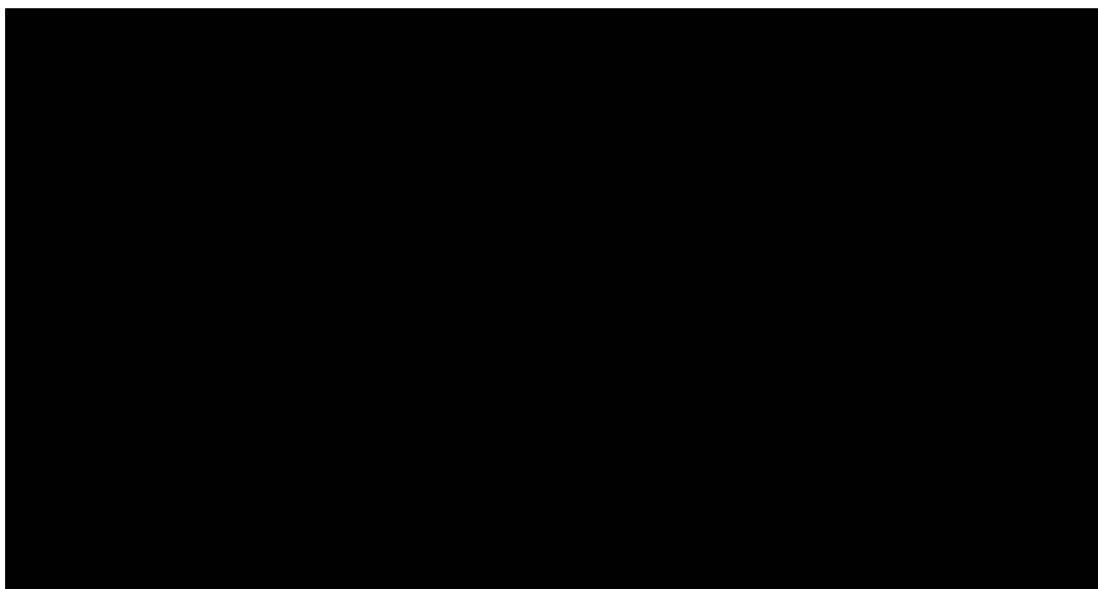
Based on the AIC and BIC statistics, the log-logistic model was the best-fitting distribution. The CS³ states that clinical advisors consulted by the company considered the exponential distribution to be the most appropriate model based on consideration of the modelled hazards and clinical plausibility. The EAG notes that the smoothed empirical hazard function increases and then decreases (see Figure 18); this pattern is not reflected by the exponential distribution which instead assumes a constant hazard. The CS also states that the predicted TTD of [REDACTED] and [REDACTED] at 3- and 5-years aligns with the experience of the Royal Marsden expanded access programme.²⁸

Table 26: AIC and BIC statistics, composite TTD+PFS (values taken from the company's additional clarification response, 4th July 2025)

Distribution	Ripretinib	
	AIC	BIC
Exponential*	721.5	723.9
Weibull	720.7	725.6
Gompertz	723.4	728.3
Log-normal	717.6	722.5
Log-logistic	714.8	719.7
Gamma	719.3	724.2
Generalised gamma	718.5	725.9
Generalised F	717.2	727.0

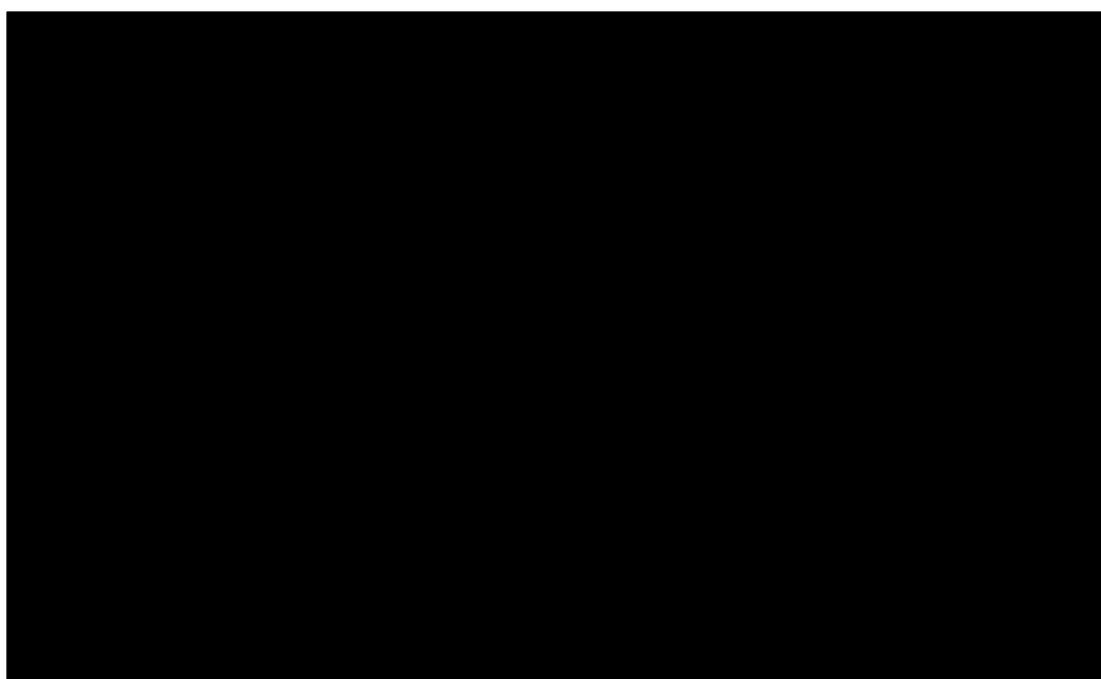
BSC - best supportive care; AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; NR - not reported
Best fitting model indicated in bold. Base case model indicated by asterisk "*"

Figure 18: Empirical and modelled hazards for ripretinib TTD+PFS (reproduced from company's additional clarification response, 4th July 2025)



AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; Gen - generalised; LL - log-likelihood.

Figure 19: Observed versus predicted TTD, ripretinib (generated by the EAG using the company's updated model)*



TTD - time to treatment discontinuation; KM - Kaplan-Meier

** Whilst the CS indicates that the company's survival analysis of TTD+PFS included the gamma and generalised F models, these survival distributions are not included in the executable model*

PFS

AIC and BIC statistics for the fitted PFS models are summarised in Table 27. Plots of the empirical and modelled hazard functions for PFS for the ripretinib and BSC groups are shown in Figure 20 and Figure 21, respectively. Comparisons of the observed Kaplan-Meier survival functions and parametric survival model predictions for PFS for the ripretinib and BSC groups are shown in Figure 22 and Figure 23, respectively.

Based on the AIC and BIC statistics, the log-normal distribution was the best-fitting model in the ripretinib group, whilst the log-logistic distribution was the best-fitting model in the BSC group. When combined (based on the sum of the AIC/BIC statistics across both treatment groups), there was little difference in goodness-of-fit between the log-normal and log-logistic distributions. The company selected the log-normal distribution for inclusion in the base case analysis for both treatment groups. The CS³ states that this distribution was selected because: (i) it was the best-fitting model based on AIC and BIC in the ripretinib group; (ii) it is amongst the best-fitting models based on combined AIC and BIC and (iii) it provides a good visual fit to the observed data. The CS also notes that the log-normal model leads to a more conservative estimate of 3-year PFS for ripretinib compared with the log-logistic distribution (█████ versus █████, respectively).

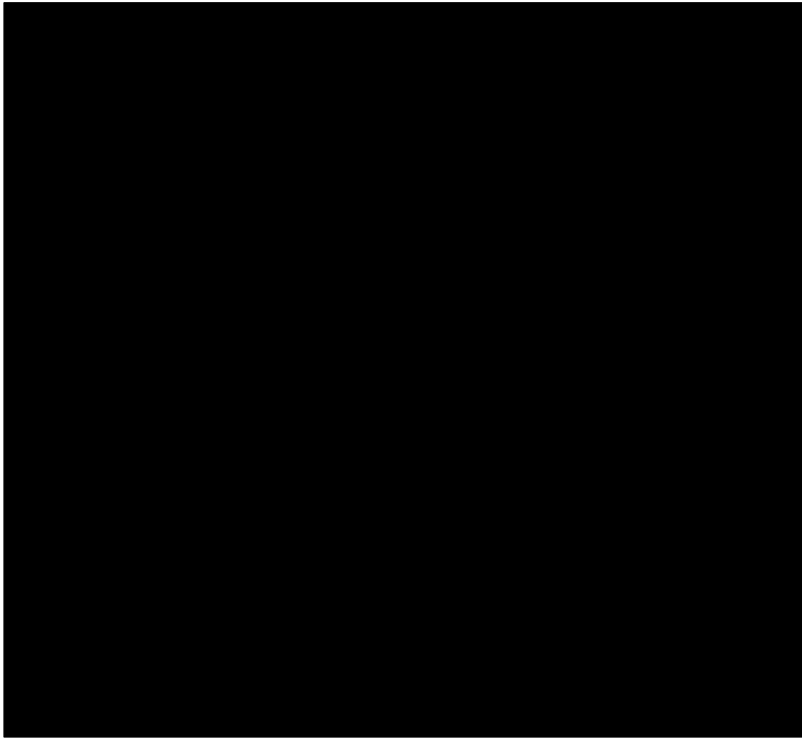
The CS³ does not present the hazard functions for PFS. Based on the plots provided in TA881¹ (Figure 20 and Figure 21), the EAG notes that within the ripretinib group, the hazard initially increases, decreases, plateaus and increases again, whereas in the BSC group, the hazard increases, decreases and increases again. Neither the selected log-normal model nor any of the other standard parametric models are able to fully reflect the shape of the smoothed empirical hazard functions.

Table 27: AIC and BIC statistics, PFS (adapted from CS, Table 30)

Distribution	Ripretinib		BSC		Combined	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	460.51	462.95	127.72	129.50	588.23	592.45
Weibull	461.10	465.98	127.71	131.28	588.81	597.26
Gompertz	462.47	467.36	128.99	132.55	591.46	599.91
Log-normal*	457.14	462.03	112.57	116.13	569.71	578.16
Log-logistic	459.57	464.46	109.61	113.17	569.18	577.63
Generalised gamma	458.75	466.08	112.01	117.37	570.77	583.45

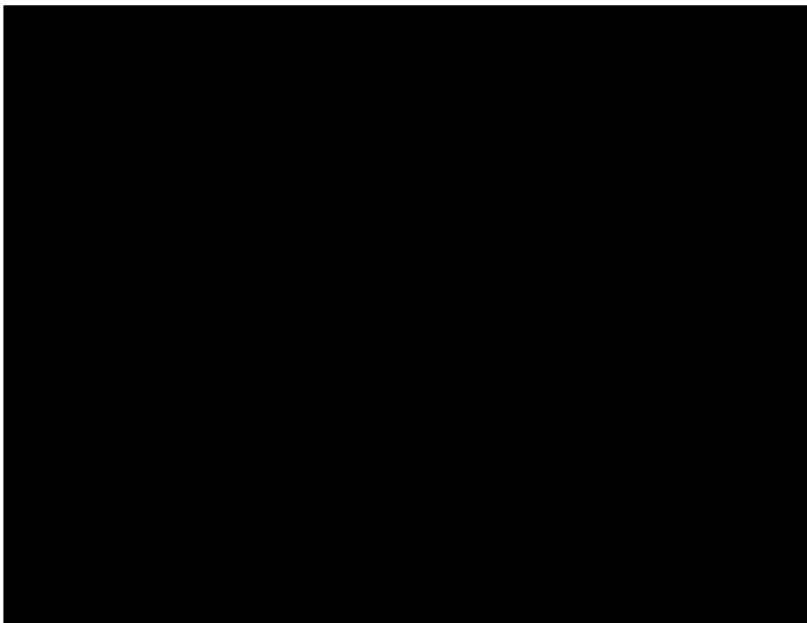
BSC - best supportive care; AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion
Best fitting model indicated in bold. Base case model indicated by asterisk "*"

Figure 20: Smoothed, unsmoothed and modelled hazard functions for PFS, ripretinib (reproduced from TA881 clarification response, Figure 4)



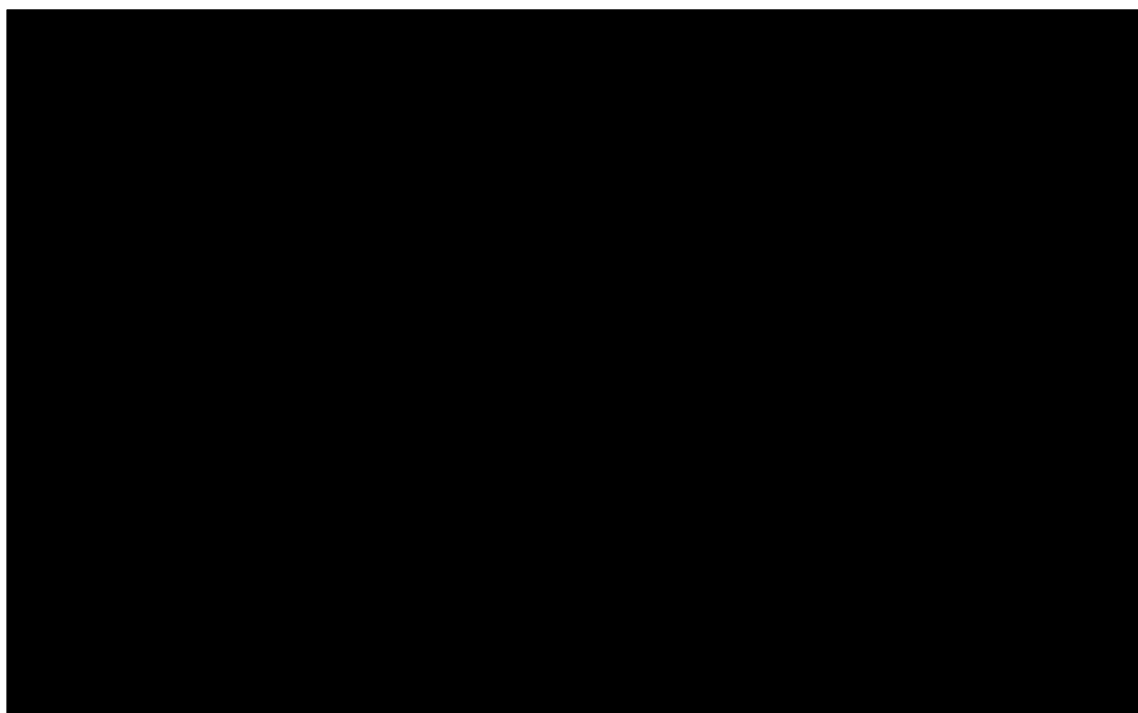
Gen - generalised; PFS - progression-free survival

Figure 21: Smoothed, unsmoothed and modelled hazard functions for PFS, BSC (reproduced from TA881 clarification response, Figure 5)



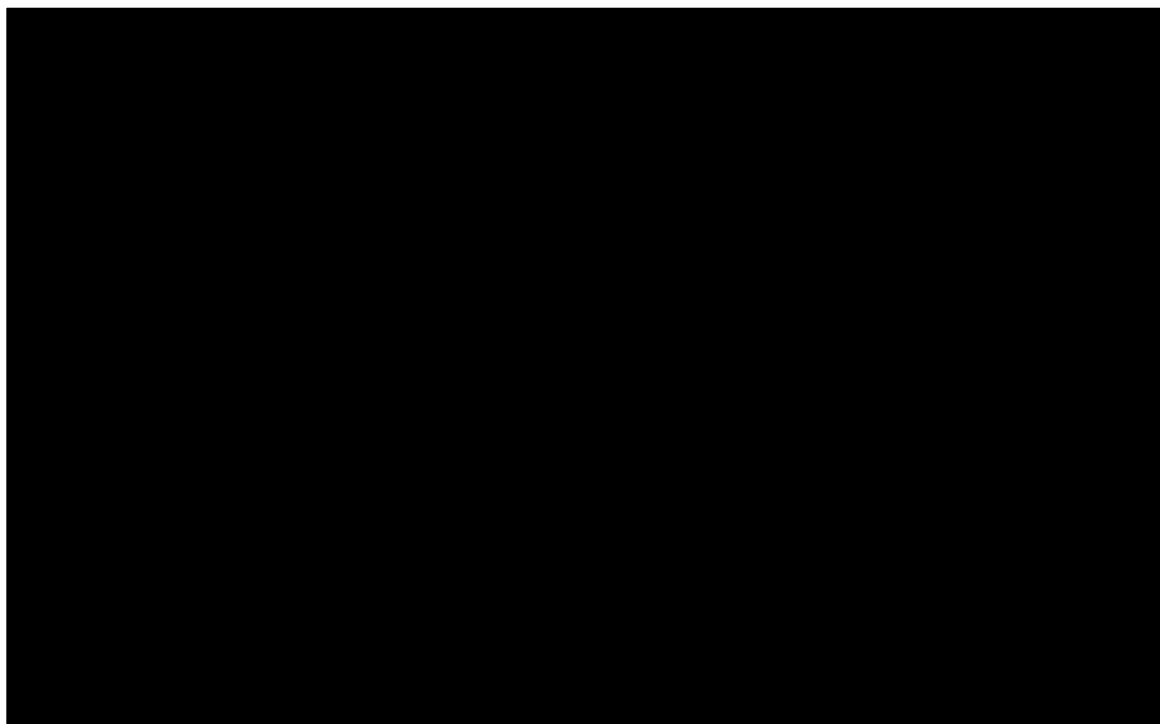
Gen - generalised; PFS - progression-free survival; BSC - best supportive care

Figure 22: Observed versus predicted PFS, ripretinib (generated by the EAG using the company's model)



PFS - progression-free survival; KM - Kaplan-Meier

Figure 23: Observed versus predicted PFS, BSC (generated by the EAG using the company's model)



PFS - progression-free survival; BSC - best supportive care; KM - Kaplan-Meier

OS

AIC and BIC statistics for the fitted models are summarised in Table 28. Plots of the empirical and modelled hazard functions for OS for the ripretinib and BSC groups are shown in Figure 24 and Figure 25, respectively. Comparisons of the observed Kaplan-Meier survival functions and parametric survival model predictions for OS for the ripretinib and BSC groups are shown in Figure 26 and Figure 27, respectively. All OS data presented in this section include treatment switching adjustment in the BSC group.

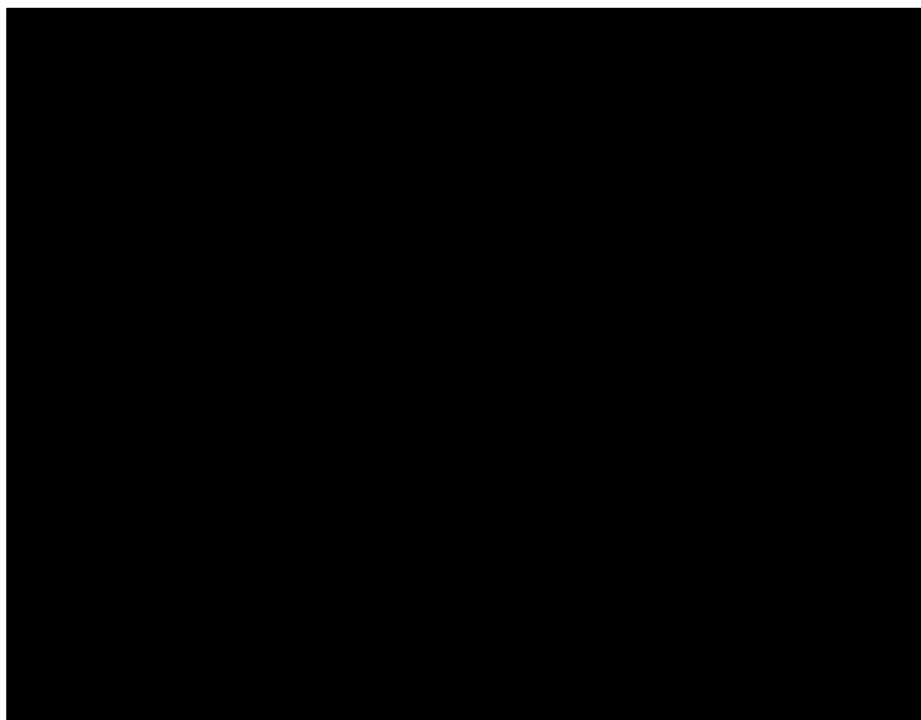
Based on the AIC, the log-normal distribution was the best-fitting model in the ripretinib group, whereas the log-logistic distribution was the best-fitting model in the BSC group. Based on the BIC, the exponential model was the best-fitting model in the ripretinib group whereas the log-logistic model was the best-fitting model in the BSC group. When combined (based on the sum of the AIC/BIC across both groups), the log-logistic model had the lowest AIC and BIC. The company selected the log-logistic distribution for inclusion in the base case model. The CS³ states that 10-year predicted OS for the log-logistic model is ■■■■ “which is in line with the upper end of estimates stated at a clinical advisory board held in July 2024.”³ The CS also states that clinical advisors attending the 2024 advisory board meeting⁴⁰ generally agreed that the shape of the log-logistic hazard function, which initially increases and then decreases (see Figure 24 and Figure 25), would be reflective of clinical reality. The CS further justifies the predicted 9-year OS estimate of 10% for ripretinib based on the view that 10-year OS for second-line sunitinib is 10% and that patients typically progress quickly (within 6-9 months) on both second-line sunitinib and third-line regorafenib.

Table 28: AIC and BIC statistics, OS (adapted from CS, Table 33)

Distribution	Ripretinib		BSC		Combined	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	415.08	417.52	137.48	139.26	552.55	556.78
Weibull	416.92	421.81	134.72	138.29	551.64	560.10
Gompertz	416.66	421.54	137.24	140.81	553.90	562.35
Log-normal	414.14	419.03	134.49	138.06	548.63	557.09
Log-logistic*	414.15	419.04	133.23	136.80	547.38	555.83
Generalised gamma	416.10	423.43	135.89	141.25	551.99	564.67

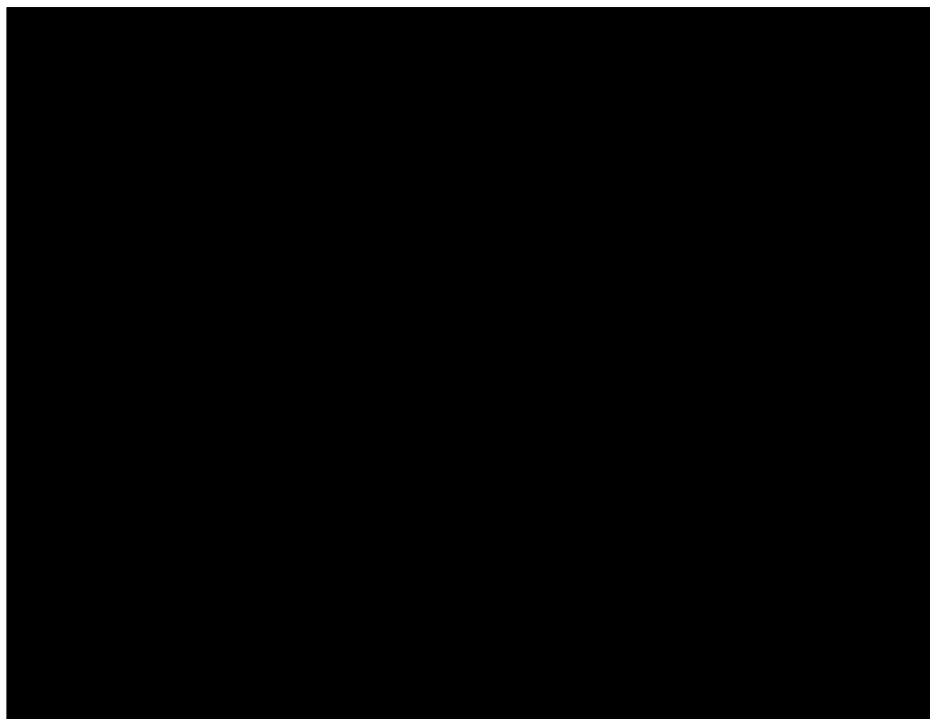
BSC - best supportive care; AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion
Best fitting model indicated in bold. Base case model indicated by asterisk “*”

Figure 24: Smoothed, unsmoothed and modelled hazard functions for OS, ripretinib (reproduced from TA881 additional clarification response, Figure 1)



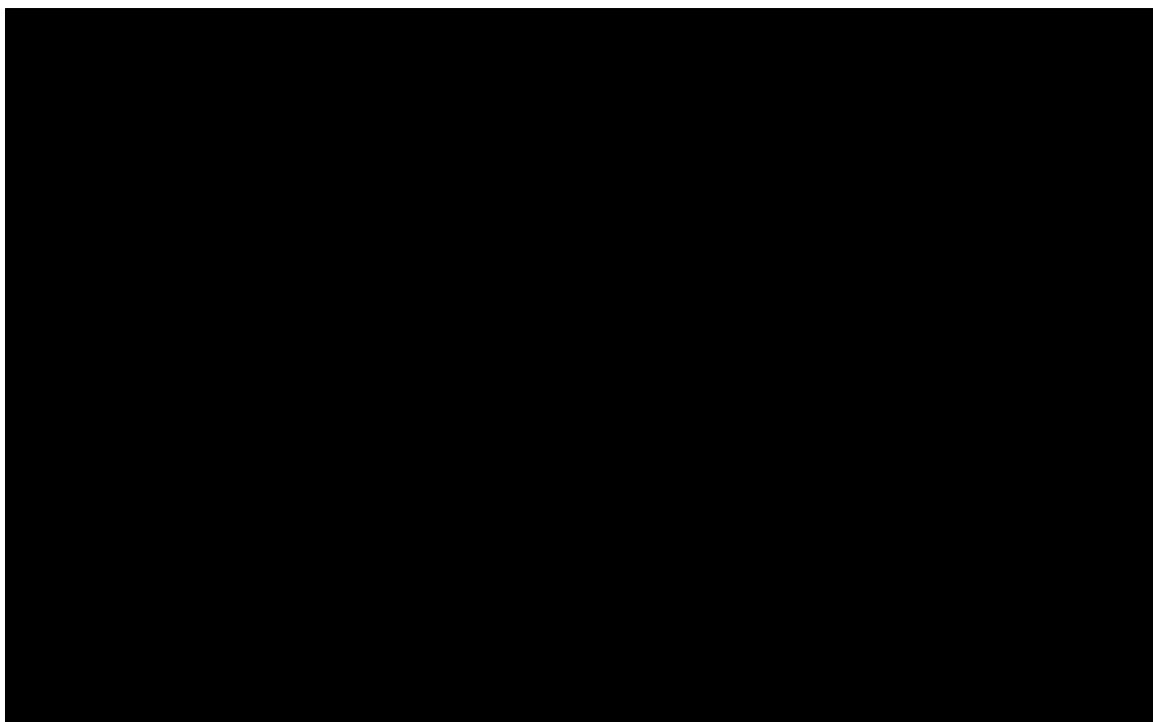
Gen - generalised; OS - overall survival.

Figure 25: Smoothed, unsmoothed and modelled hazard functions for OS, BSC, includes switching adjustment (reproduced from TA881 clarification response, Figure 7)



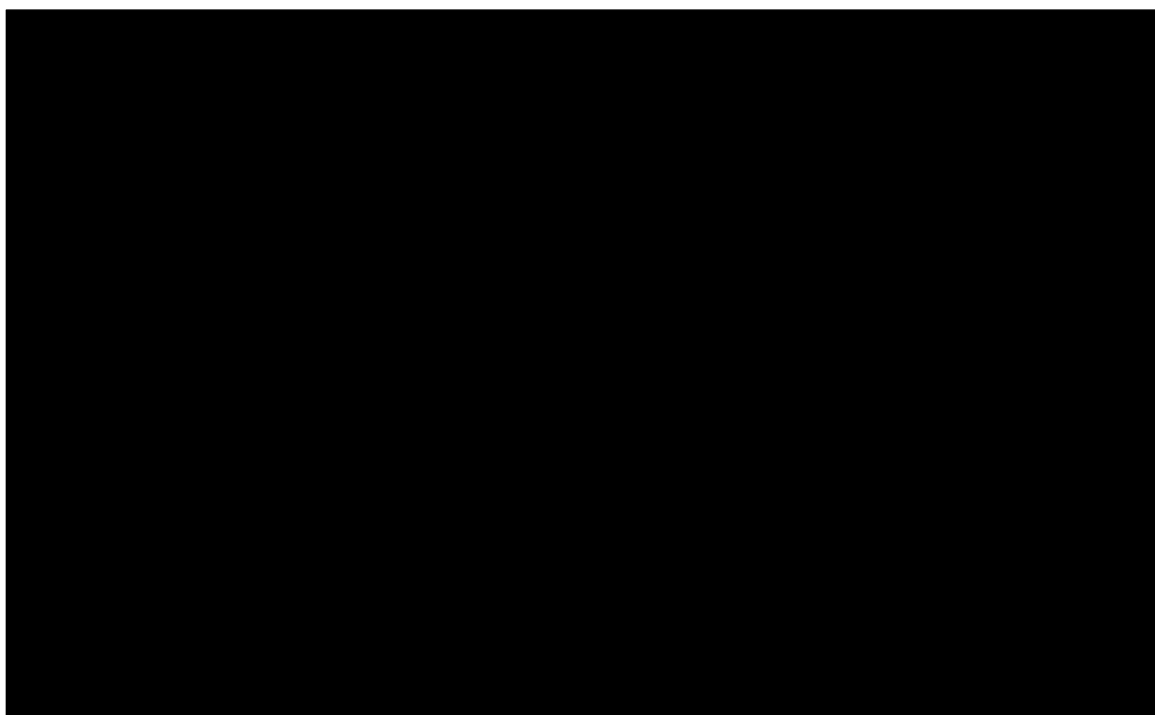
BSC - best supportive care; Gen - generalised; OS - overall survival.

Figure 26: Observed versus predicted OS, ripretinib (generated by the EAG using the company's model)



OS - overall survival; KM - Kaplan-Meier

Figure 27: Observed versus predicted OS, BSC, includes switching adjustment (generated by the EAG using the company's model)



BSC - best supportive care; OS - overall survival; KM - Kaplan-Meier

Whilst the company's base case model does not include any adjustment of the INVICTUS data³⁵ to account for the effect of IPDE to ripretinib 150mg BID on OS, the CS³ presents the results of several alternative approaches which attempt to account for this source of potential confounding. The results of these analyses are presented in Table 41.

Summary of predictions of selected parametric survival models for TTD, PFS and OS

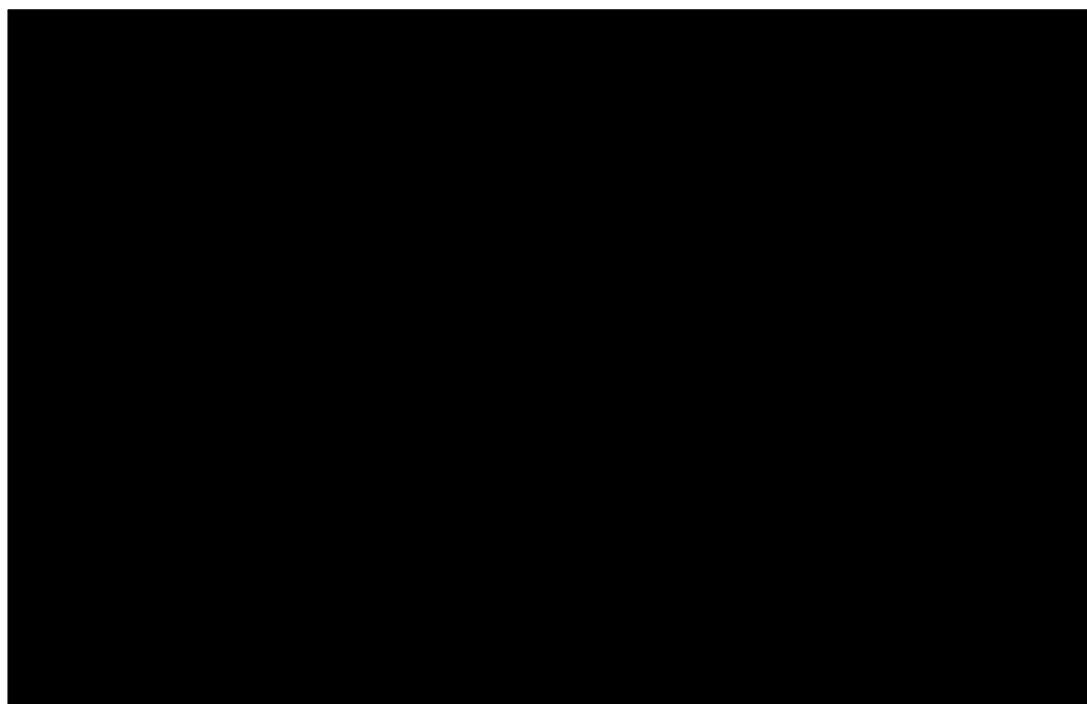
The parametric survival models applied in the company's base case analysis are summarised in Table 29. The overall model predictions of TTD, PFS and OS in the company's base case model are presented together in Figure 28. As shown in the figure, ripretinib is predicted to improve both PFS and OS compared to BSC. Ripretinib TTD is predicted to be greater than PFS. The EAG has concerns regarding the clinical plausibility of the company's model predictions of OS for the ripretinib group; these concerns are discussed in Section 5.3.5.

Table 29: Summary of company's base case parametric survival models for TTD, PFS and OS

Treatment group	End point	Base case model selection
Ripretinib	TTD+PFS	Exponential
	PFS	Log-normal
	OS	Log-logistic
BSC	PFS	Log-normal
	OS	Log-logistic

TTD - time to treatment discontinuation; PFS - progression-free survival; OS - overall survival; BSC - best supportive care

Figure 28: Company's base case model predictions of TTD, PFS and OS*



BSC - best supportive care; Rip - ripretinib; TTD - time to treatment discontinuation; PFS - progression-free survival; OS - overall survival

** Includes general population mortality constraints (including the correction of the error in company's OS constraint)*

4.2.4.2 Health-related quality of life

Health state utility values

Health state utility values were informed by EQ-5D-5L data collected in INVICTUS.² According to the CS,³ EQ-5D-5L data were collected using an electronic PRO system at Cycle 1 on Day 1 and Day 15, on Day 1 of subsequent treatment cycles, and within 7 days after the last dose, at the end of treatment visit. EQ-5D-5L utility scores were calculated using the algorithm based on country-specific reference score sets reported by Van Hout *et al.*⁶⁴ The EQ-5D-5L data were then mapped to the 3L version using the algorithm reported by Hernández Alava and Pudney.⁷¹ Utility values for each model health state were based on the least squares mean (LSM) values from a mixed model for repeat measures (MMRM) analysis conducted by the company, which included treatment arm, treatment status, health state (PF/PD) and two-way and three-way interactions for these items as fixed effects. The CS states that the analysis used a “*compound symmetry within-subject correlation structure per treatment arm/treatment status/health state combination.*” The company’s response to clarification question B14 states that treatment switching in the placebo treatment arm was formally incorporated in the MMRM model, but that dose escalation to ripretinib 150mg BID was not included.³⁵ The company’s clarification response also states that the chosen model was the only MMRM model considered; however, it was considered “*the most parsimonious MMRM model that would allow for full flexibility in health state utility estimations, whilst avoiding the potential risk of over fitting.*”

The CS³ reports that the dataset used to inform health state utility values included “*all EQ-5D measurements taken while patients were within each partition of the model.*” The company’s clarification response (question B14)³⁵ presents the number of visits and patients by health status and treatment group which informed the MMRM analysis (see Table 30). Information regarding any exclusions of patients or time points, or imputation methods used to handle missing data are not mentioned in either the CS or the clarification response. As shown in the table, very few data points were available for patients with progressed disease who were not receiving ripretinib (N visits = 46; N patients = 43).

Table 30: Summary of data used to inform MMRM for health state utility values (adapted from clarification response, Table 14)

State	Number of visits	Number of patients
Progression-free	924	126
Progressed disease (BSC)	46	43
Progressed disease (ripretinib, on treatment)	550	79
Progressed disease (ripretinib, off treatment)	46	43

BSC - best supportive care

Based on the MMRM, the company’s economic model applies utility values of 0.722 for the progression-free state and separate values for the progressed disease state, based on treatment group

and treatment status: 0.699 for ripretinib patients whilst they are on post-progression treatment, and 0.624 for patients who have discontinued ripretinib and for patients receiving BSC (see Table 31). Despite the low numbers of visits/patients in the PD states and the presence of some minor discrepancies in the company's approach to calculating utility estimates using the coefficients and formula provided in clarification response B14,³⁵ the EAG's clinical advisors considered the utility values applied in all model health states to be clinically plausible. The company's economic model includes the adjustment of utility values for increasing age using EQ-5D-3L estimates for the UK general population estimates reported by Hernández Alava *et al.*⁷²

Table 31: Health state utility values applied in the company's base case model

Health state	Mean utility (SD)		Source
	Ripretinib	BSC	
Progression-free	0.722 (0.217)		EQ-5D-5L estimates from INVICTUS ² (mapped to 3L version using Hernández Alava <i>et al.</i> ⁷¹)
Progressed disease (on treatment)	0.699 (0.218)	0.624 (0.284)	
Progressed disease (off treatment)	0.624 (0.284)		

BSC - best supportive care; EQ-5D-5L - Euroqol 5-Dimensions 5-Level; 3L - 3 level; SD - standard deviation

Disutility values associated with adverse events

The company's model includes QALY losses associated with Grade ≥ 3 TEAEs occurring with an incidence of $\geq 5\%$ in either treatment group during the double-blind phase of INVICTUS.³ Disutility values for AEs were taken from external sources. The AE frequencies and disutility values applied in the model are shown in Table 32. The disutility for anaemia was based on a Short Form 6-Dimensions (SF-6D) value reported by Harrow *et al.*,⁶² which, according to the CS,³ was then re-scaled to the EQ-5D using a method previously described by Hoyle *et al.*⁷³ Despite scrutinising each of these sources, the EAG was unable to determine how this re-scaling was done or how the resulting disutility value was estimated. The disutility value for abdominal pain was based on an EQ-5D VAS estimate for chest pain in people with lung cancer reported by Doyle *et al.*⁶³ The CS states that the disutility for hypertension was also taken from Doyle *et al.*, although the EAG notes that this study does not report values for this type of AE; it appears that the company has assumed that the disutility for hypertension is equivalent to that for chest pain. Whilst this assumption has been applied in previous appraisals (e.g., NICE TA439⁷⁴), the justification for assuming hypertension and chest pain have equivalent HRQoL impacts is unclear. Overall disutilities attributable to AEs were estimated to be 0.019 for ripretinib, and 0.015 for BSC. Based on the description of the model in the CS, the company had intended to apply AE-related QALY losses in the first model cycle based on an assumed duration of 28 days; however, the model is subject to an error whereby the QALY loss is applied in every model cycle (see Section 4.3.5, critical appraisal point 1).

Table 32: AE disutility values and total disutilities applied in the company's base case model, by treatment group

AE	Frequency		Disutility (SD)	Source and method	Total disutility	
	Ripretinib	BSC			Ripretinib	BSC
Anaemia	0.106	0.140	0.085 (NR)	Harrow <i>et al.</i> ⁶² - SF-6D disutility in WHI survey rescaled to EQ-5D*	0.008	0.012
Abdominal pain	0.071	0.047	0.069 (NR)	Doyle <i>et al.</i> ⁶³ - EQ-5D VAS for hypothetical lung cancer states valued by 101 members of the general population	0.005	0.003
Hypertension	0.071	0.000	0.069 (NR)		0.005	0.000
Mean overall disutility					0.019	0.015

AE - adverse event; BSC - best supportive care; NR - not reported; SD - standard deviation; EQ-5D - Euroqol 5-Dimensions; SF-6D - Short Form 6-Dimensions; VAS - visual analogue scale; WHI - Women's Health Initiative; NR - not reported

*Derivation methods unclear from CS³

4.2.4.3 Resource use and costs

The model includes the following cost components: (i) drug acquisition costs associated with ripretinib and BSC (pain management medications); (ii) health state costs; (iii) pre-treatment costs; (iv) palliative treatment costs; (v) AE management costs and (vi) end-of-life care costs. A summary of the model cost parameters is shown in Table 33. The derivation of these costs is presented in further detail in the sections below.

Table 33: Summary of model cost parameters

Description	Ripretinib	BSC	EAG comments
Ripretinib drug acquisition cost (per pack [30 days' supply]), excludes RDI adjustment	List price £18,400.00 PAS price [REDACTED]	N/a	The model includes an RDI of 0.965 based on INVICTUS. ² Wastage is modelled using a pack-based approach.
BSC costs, PF state (per 28-day cycle)	£20.26		Based on drug usage from physician survey used in TA488 ⁴⁵ and dosing assumptions from TA730. ⁶⁵ Drug costs taken from BNF. ²⁶
BSC costs, PD state (per 28-day cycle)	On ripretinib: £0.00 On BSC: £30.24	£30.24	
Health state costs, PF state (per 28-day cycle)	£202.79	£163.65	Resource use based on physician survey used to inform TA488 ⁴⁵ and TA730. ⁶⁵ Unit costs from NHS Cost Collection 2023/24. ⁶⁷
Health state costs, PD state (per 28-day cycle)*	£233.64		
Pre-treatment costs (once-only in the first cycle)	£129.93	£33.98	

Description	Ripretinib	BSC	EAG comments
Palliative RT and palliative resection costs (applied in the first cycle and on progression)	£682.23		
AE management costs (applied once-only in first cycle)	£207.08	£170.46	AE frequencies from INVICTUS. ² Unit costs from NHS Cost Collection. ⁶⁷
End-of-life costs (applied once-only on death)	£10,926.76		Taken from NICE TA488 ⁴⁵ and inflated to current prices using HCHS/ NHSCII indices. ⁶⁹

BSC - best supportive care; PAS - Patient Access Scheme; RDI - relative dose intensity; PF - progression-free; PD - progressed disease; TA - Technology Appraisal; AE - adverse event; RT - radiotherapy; HCHS - Hospital and Community Health Services; NHSCII - NHS Cost Inflation Index; N/a - not applicable

* Applies to progressed ripretinib patients whilst receiving treatment and after discontinuation

Drug acquisition costs (per cycle, ripretinib group only)

The list price per pack of 90 x 50mg ripretinib tablets is £18,400.00 (30 days' supply). The total acquisition costs for ripretinib are calculated in the model as a function of the list price of ripretinib, the probability of remaining on treatment in each cycle (based on the TTD function), the number of days per cycle, and a mean RDI of [REDACTED] from INVICTUS.² Wastage is calculated using an integer pack-based approach which tracks whether a new pack of 90 ripretinib tablets is required in each 28-day model cycle (a new pack is not required every 10 model cycles). As ripretinib is an oral therapy, no administration costs are assumed.

A Patient Access Scheme (PAS) has been agreed for ripretinib. This takes the form of a simple price discount of [REDACTED]. The acquisition cost for ripretinib per 30-day pack including the PAS is estimated to be [REDACTED].³

BSC medications (per cycle, both treatment groups)

BSC pain management costs were based on a survey of 15 physicians in England and Wales undertaken to inform TA488,⁴⁵ with additional information on dosing taken from TA730.⁶⁵ Drug costs were taken from the British National Formulary (BNF).²⁶ The most commonly prescribed dosage form of each product was determined using Prescription Cost Analysis data.⁶⁶ The CS³ states that costing was based on the maintenance doses described in the SmPC for the most common indication of each product. Where a range of doses was available, the CS states that the lowest price for each medication was used; however, the EAG notes that this is not accurate as lower prices are available for several products in the Commercial Medicines Unit (CMU) electronic Market Information Tool (eMIT) (see Section 4.3.5). A breakdown of pain management drug costs applied in the model is shown in Table 34.

Table 34: BSC (pain management) drug costs

Drug, dose	Resource use			Units per pack	Cost per pack	Units per cycle	Expected cost per 28-day cycle		
	% PF patients	% PD patients					PF	PD	
		Ripretinib (on treatment)	Ripretinib (off treatment) /BSC					Ripretinib (on treatment)	Ripretinib (off treatment) /BSC
Co-codamol, 30/500mg QDS	18.0%	0.0%	22.0%	100	£4.03	224	£1.62	£0.00	£1.99
Tramadol capsules, 100mg QDS	12.0%	0.0%	14.0%	100	£2.37	224	£0.64	£0.00	£0.74
Paracetamol tablets, 1g QDS	33.0%	0.0%	38.0%	100	£2.16	224	£1.60	£0.00	£1.84
Morphine sulfate, 30mg IR every 4 hours	20.0%	0.0%	29.0%	56	£5.31	168	£3.19	£0.00	£4.62
				56	£10.61	168	£6.37	£0.00	£9.23
Dexamethasone, 4mg OD	11.0%	0.0%	19.0%	50	£111.12	28	£6.84	£0.00	£11.82
Total cost	-	-	-	-	-	-	£20.26	£0.00	£30.24

PF - progression-free; PD - progressed disease; BSC - best supportive care; mg - milligram; QDS - four times daily; OD - once daily; IR - immediate release

Health state costs (per cycle, both treatment groups)

Health state costs are assumed to include CT and MRI scans, FBCs, LFTs and outpatient appointments. The frequency of each resource item was based on the clinician survey used to inform NICE TA488.⁴⁵ Unit costs were taken from the NHS Cost Collection 2023/24.⁶⁷ The health state costs applied in each model cycle are shown in Table 35. The currency codes shown in the table reflect those reported in the CS;³ however, the EAG notes that some of these appear to be inaccurate. These costs are applied in every cycle of the model.

Pre-treatment costs (once-only, both treatment groups)

Pre-treatment costs are assumed to include CT scans, MRI scans, FBCs and LFTs. Usage of these resource items was also taken from the clinician survey used to inform TA488.⁴⁵ Unit costs were taken from the NHS Cost Collection 2023/24.⁶⁷ Total pre-treatment costs are shown in Table 36. These costs are applied in the first model cycle only.

Palliative treatment costs (once at model entry and once on progression, both treatment groups)

The model assumes that a proportion of patients will receive palliative resection and/or palliative RT. Again, the proportions of patients receiving these treatments were taken from the physician survey used to inform TA488.⁴⁵ Unit costs were taken from the NHS Cost Collection 2023/24.⁶⁷ Total palliative treatment costs are shown in Table 37. These costs are applied to all patients in the first cycle and to patients with incident disease progression in each model cycle.

Costs of managing AEs

The model includes the costs of managing Grade 3/4 TEAEs which occurred in $\geq 5\%$ of patients in either group in INVICTUS.² Unit costs were taken from NHS Cost Collection 2023/24.⁶⁷ The expected costs of managing AEs for ripretinib and BSC are presented in Table 38. The costs of managing AEs are applied once only in the first model cycle.

Table 35: Health state costs per 28-day model cycle

Description	Unit cost	Resource use			Total cost			NHS Cost Collection codes
		Ripretinib PF	BSC PF	Both PD*	Ripretinib PF	BSC PF	Both PD*	
CT scan	£123.25	0.33	0.21	0.28	£40.74	£26.08	£34.00	Weighted mean of HRG codes RD26Z
MRI scan	£171.05	0.20	0.22	0.50	£34.38	£38.01	£85.52	Weighted mean of HRG codes RD01A, RD02A, RD03Z, RD04Z, RD05Z, RD06Z, RD07Z
Full blood count	£3.09	0.63	0.37	0.45	£1.93	£1.14	£1.41	HRG code DAPS05
Liver function test	£1.95	0.63	0.36	0.43	£1.22	£0.69	£0.83	HRG code DAPS04
Outpatient care visit	£193	0.65	0.51	0.58	£125.45	£97.72	£111.88	HRG code WF01A
Total	-	-	-	-	£202.79	£163.65	£233.64	-

CT - computed tomography, MRI - magnetic resonance imaging; BSC - best supportive care; PF - progression free; PD - progressive disease; HRG - Healthcare Resource Group

* Applies to progressed ripretinib patients whilst receiving treatment and after discontinuation

Table 36: Pre-treatment costs (applied once only in the first model cycle)

Description	Unit cost	Prop of patients		Expected cost		NHS Cost Collection codes
		Ripretinib	BSC	Ripretinib	BSC	
CT scan	£123.25	0.85	0.24	£104.76	£29.58	Weighted mean of HRG codes RD26Z
MRI scan	£171.05	0.12	0.01	£20.53	£1.71	Weighted mean of HRG codes RD01A-RD07Z
Full blood count	£3.09	0.92	0.56	£2.85	£1.73	HRG code DAPS05
Liver function test	£1.95	0.92	0.49	£1.79	£0.95	HRG code DAPS04
Total	-	-	-	£129.93	£33.98	-

CT - computed tomography, MRI - magnetic resonance imaging; BSC - best supportive care; HRG - Healthcare Resource Group

Table 37: Palliative treatment costs (applied once to all patients in the first model cycle and again at disease progression)

Description	Unit cost	Proportion of patients		Expected cost		NHS Cost Collection codes
		PF	PD	PF	PD	
Palliative surgical resection	£6,090.28	0.10	0.10	£609.03	£609.03	Weighted mean of HRG codes FD11D, FD11E and FD11F
Palliative radiotherapy	£366.00	0.20	0.20	£73.20	£73.20	Weighted mean of HRG codes SD01A, SD02A, SD03A and SD04A
Total	-	-	-	£682.23	£682.23	-

PF - progression-free; PD - progressed disease; HRG - Healthcare Resource Group

Table 38: Costs of managing AEs (applied once only in the first model cycle)

AE	Unit cost	Frequency		Expected cost		NHS Cost Collection codes
		Ripretinib	BSC	Ripretinib	BSC	
Anaemia	£989.48	0.1060	0.1400	£104.88	£138.53	Weighted mean of HRG codes SA01G to SA01K; SA03G to SA03H; SA04H to SA04L; SA05G to SA05J
Abdominal pain	£679.32	0.0710	0.0470	£48.23	£31.93	Weighted mean of HRG codes FD05A and FD05B
Hypertension	£760.02	0.0710	-	£53.96	-	HRG code EB04Z
Total	-	-	-	£207.08	£170.46	-

AE - adverse event; BSC - best supportive care; HRG - Healthcare Resource Group

End-of-life care costs

The costs of end-of-life care were taken from Abel *et al.*⁶⁸ The proportions of people dying in hospital or elsewhere and the costs of death by location were used to generate a weighted cost of death (see Table 39). The reported costs were uplifted to current values using Hospital and Community Health Service (HCHS) indices and NHS Cost Inflation Indices (NHSCII).⁶⁹ The weighted cost of end-of life-care is applied to the number of new patients dying in each model cycle.

Table 39: End-of-life care costs

Description	Proportion of patients	Cost
Death in hospital	0.16	£14,856.09
Death elsewhere	0.84	£10,163.52
Weighted cost	-	£10,926.76

A scenario analysis was conducted in which end-of-life costs were taken from Round *et al.*⁷⁵ (see Table 41).

4.2.5 Model evaluation methods

The CS³ presents ICERs for ripretinib versus BSC using both the deterministic and probabilistic versions of the model. The probabilistic ICER is based on 1,000 Monte Carlo samples. The results of the probabilistic sensitivity analysis (PSA) are presented using a cost-effectiveness plane and cost-effectiveness acceptability curves (CEACs). All model results presented in the CS include the PAS-discounted price for ripretinib and the list prices for other treatments. All ICERs presented in the CS include a decision modifier of 1.7 which is consistent with estimates obtained using the York QALY Shortfall Calculator.⁷⁶

The CS³ presents the results of deterministic sensitivity analyses (DSAs) using a tornado plot and in tabular form. The CS also presents the results of 36 scenario analyses which explore the impact of: alternative discount rates; end-of-life care costs from Round *et al.*;⁷⁵ alternative parametric survival models for OS, PFS and TTD; alternative placebo group switching adjustment methods; alternative utility values; alternative methods for adjusting for the effect of IPDE on ripretinib OS and the inclusion of the costs of ripretinib 150mg BID dosing applied to 50% of the time spent receiving post-progression ripretinib (based on a clinical input rather than the proportion observed in INVICTUS²).

4.2.6 Company's cost effectiveness results

4.2.6.1 Company's central estimates of cost-effectiveness

Table 40 presents the central estimates of cost-effectiveness generated using the company's original submitted model. All ICERs include the proposed PAS for ripretinib and a decision modifier of 1.7 (unless otherwise stated). The probabilistic version of the model suggests that ripretinib is expected to generate an additional [REDACTED] discounted QALYs at an additional cost of [REDACTED]. The corresponding

ICER including a decision modifier of 1.7 is £29,826 per QALY gained. The deterministic version of the model results in a lower ICER of £28,836 per QALY gained.

Table 40: Company's base case results, ripretinib versus BSC (generated by the EAG using the company's original submitted model)

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER (excl. DM)	ICER (incl. DM)
Probabilistic model								
Ripretinib	NR			NR			£50,703	£29,826
BSC	NR			-	-	-	-	
Deterministic model								
Ripretinib	3.86			3.48			£49,021	£28,836
BSC	0.38			-	-	-	-	-

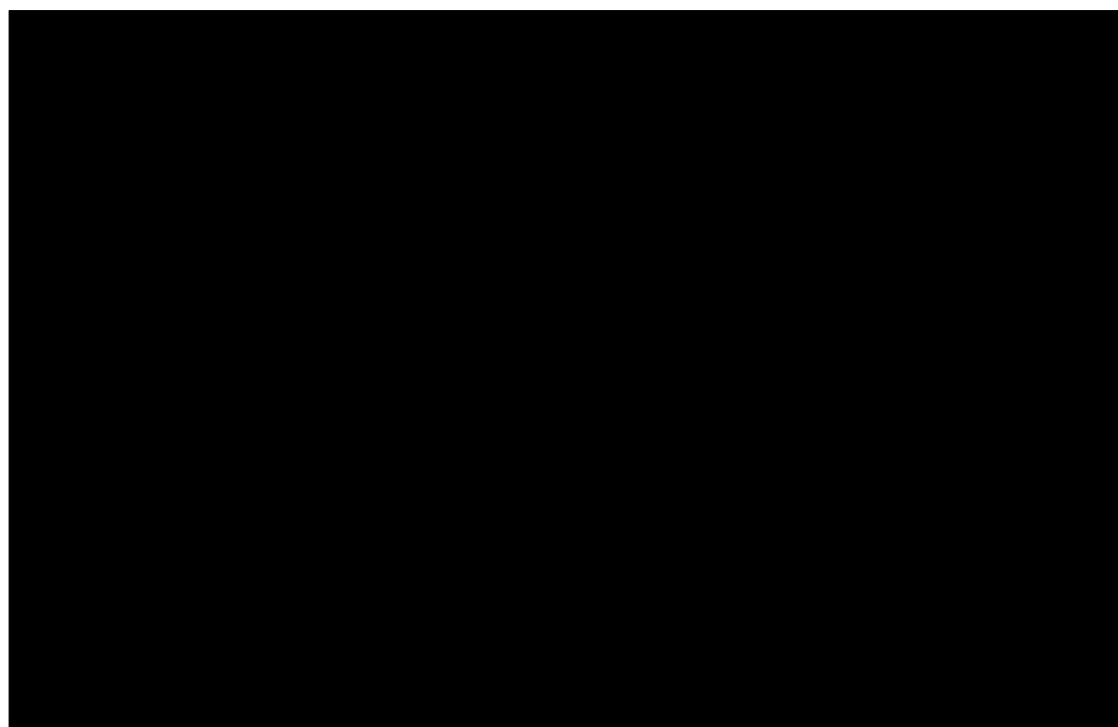
**Undiscounted*

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; DM - decision modifier; BSC - best supportive care; NR - not reported

4.2.6.2 Company's PSA results

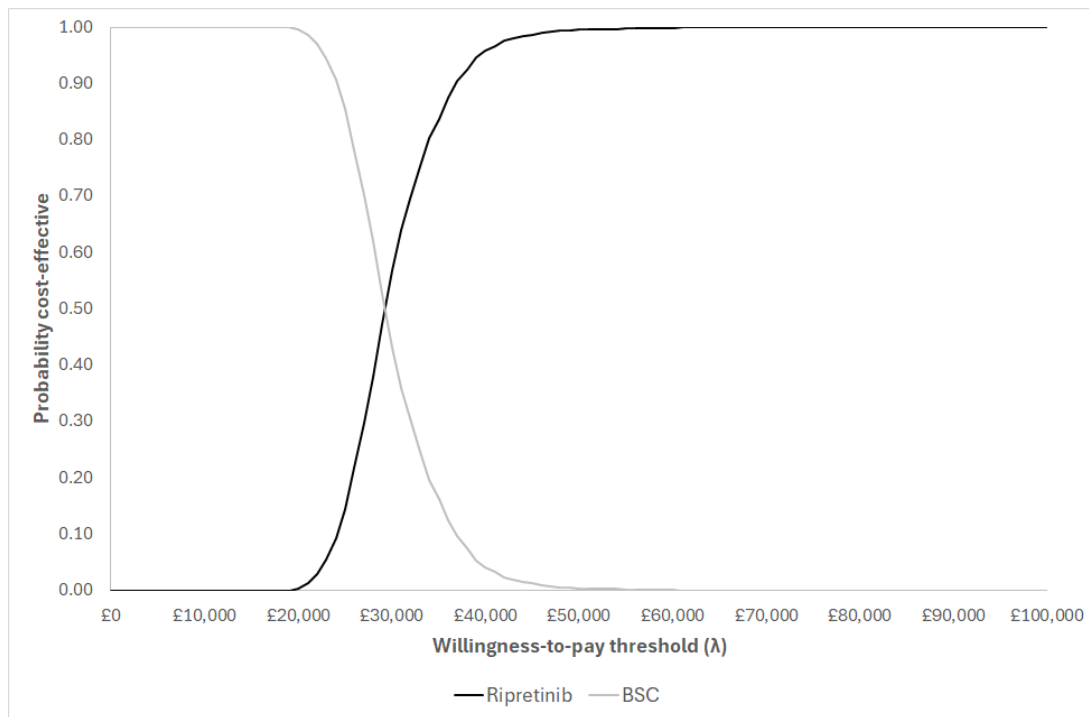
The results of the company's PSA are presented as a cost-effectiveness plane in Figure 29 and as CEACs in Figure 30; both figures include QALY weighting based on a decision modifier of 1.7. Assuming willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY gained, the probability that ripretinib generates more net benefit than BSC is expected to be approximately zero and 0.64, respectively.

Figure 29: Cost-effectiveness plane, ripretinib versus BSC, includes decision modifier of 1.7 (drawn by the EAG)



BSC - best supportive care; QALY - quality-adjusted life year

Figure 30: Cost-effectiveness acceptability curves, ripretinib versus BSC, includes decision modifier of 1.7 (drawn by the EAG)

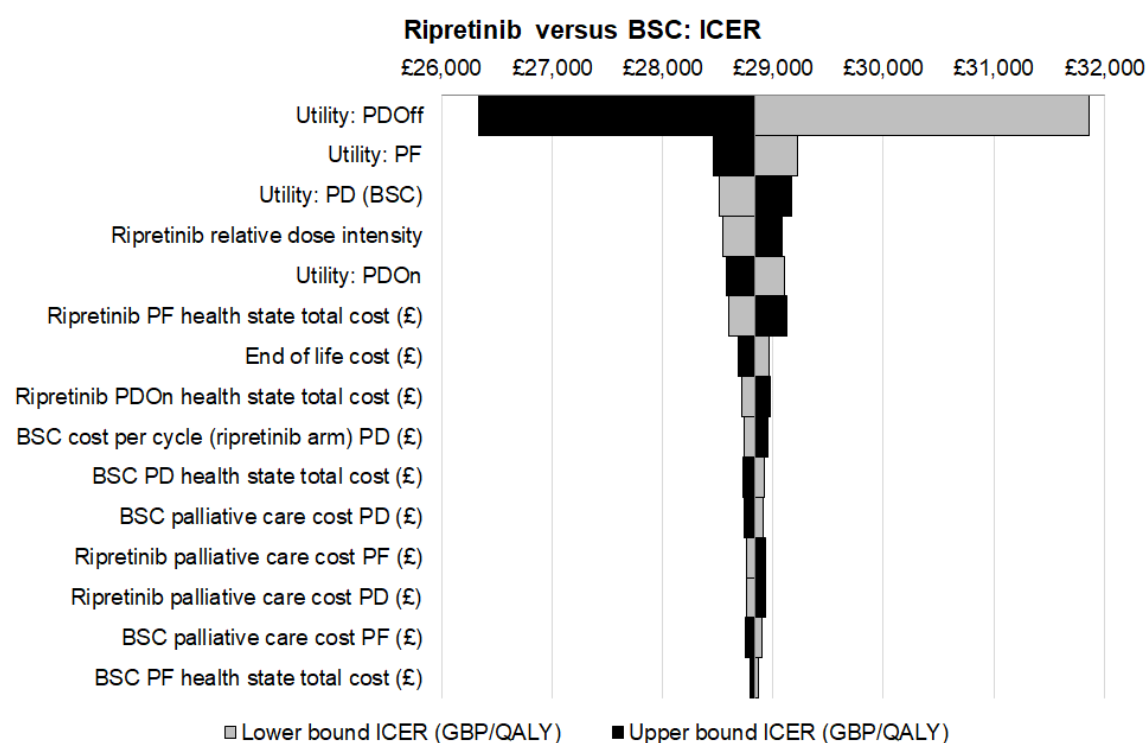


BSC - best supportive care

4.2.6.3 Company's DSA results

Figure 31 presents the results of the company's DSAs using a tornado plot. The company's DSAs indicate that the results are sensitive to the utility value applied to patients who have progressed and discontinued ripretinib ("utility: PDOff"). Across all DSAs, the ICER for ripretinib versus BSC ranges from £26,333 to £31,865 per QALY gained.

Figure 31: Tornado diagram, ripretinib versus BSC, includes decision modifier of 1.7 (generated by the EAG using the company's model)



BSC - best supportive care; ICER - incremental cost-effectiveness ratio; PF - progression -free; PD - progressed disease; PDOff - progressed disease off treatment; PDOOn - progressed disease on treatment

Note: Whilst the parameters "Utility: PDOff" and "Utility: PD (BSC)" reflect the same utility value, these parameters have a differential impact in the DSAs because the former is applied to ripretinib discontinuers whereas the latter is applied to all BSC-treated patients with progression (see clarification response,³⁵ question B21).

4.2.6.4 Company's scenario analyses results

Table 41 presents the results of the company's scenario analyses. These analyses indicate that the ICER for ripretinib is sensitive to the selected parametric survival models for TTD and OS and whether the BSC group OS is adjusted for treatment switching. The analyses indicate that the model is not sensitive to the approaches used to adjust OS to account for IPDE in the ripretinib group in the CS³ (Scenarios S30 to S35) or to the inclusion of BID dosing costs (applied to 50% of post-progression treatment time). Across all of the scenario analyses, the ICER for ripretinib versus BSC ranges from £24,851 per QALY gained (Scenario S1: discount rates = 0%) to £61,731 per QALY gained (Scenario S19: placebo group OS unadjusted).

Table 41: Company's scenario analysis results, ripretinib versus BSC, original submitted model (generated by the EAG using the company's model)

Scenario no.	Scenario description	Inc. QALYs	Inc. Costs	ICER (excl. DM)	ICER (incl. DM)
-	Base case (deterministic)			£49,021	£28,836
Discounting and end-of-life care costs					
S1	Discount rates = 0%			£42,247	£24,851
S2	Discount rates = 6%			£52,953	£31,149
S3	End-of-life care cost from Round <i>et al.</i> ⁷⁵			£49,197	£28,939
OS models					
S4	OS – exponential			£78,625	£46,250
S5	OS – Weibull			£63,923	£37,602
S6	OS – Gompertz			£44,620	£26,247
S7	OS – log-normal			£47,900	£28,176
S8	OS – generalised gamma			£49,255	£28,974
PFS models					
S9	PFS – exponential			£48,638	£28,611
S10	PFS – Weibull			£48,627	£28,604
S11	PFS – Gompertz			£48,688	£28,640
S12	PFS – log-logistic			£51,133	£30,079
S13	PFS – generalised gamma			£48,701	£28,648
TTD models					
S14	TTD – Weibull			£48,746	£28,674
S15	TTD – Gompertz			£49,196	£28,939
S16	TTD – log-normal			£54,557	£32,092
S17	TTD – log-logistic			£56,929	£33,487
S18	TTD – generalised gamma			£49,812	£29,301
Placebo group switching adjustment					
S19	OS: Unadjusted*			£74,077	£61,731
S20	OS: two-stage adjusted simple without re-censoring			£49,088	£28,876
S21	OS: two-stage adjusted complex without re-censoring			£50,988	£29,993
S22	OS: two-stage adjusted complex with re-censoring			£50,618	£29,775
S23	OS: RPSFTM-adjusted without re-censoring			£50,535	£29,727

Scenario no.	Scenario description	Inc. QALYs	Inc. Costs	ICER (excl. DM)	ICER (incl. DM)
S24	OS: RPSFTM-adjusted with re-censoring			£48,004	£28,237
S25	OS: RPSFTM-adjusted with common treatment effect relaxed ($k_i=0.5$; Weibull)			£46,699	£27,470
S26	OS: RPSFTM-adjusted with common treatment effect relaxed ($k_i=0.5$)			£52,877	£31,104
Utility values					
S27	GRID utility (0.647) for progressed disease (BSC) and progressed disease on-treatment			£47,932	£28,195
S28	GRID utility (0.647) for all progressed disease partitions			£48,398	£28,469
S29	Same utility in progressed on- and off-treatment partitions (0.624 from INVICTUS ²)			£49,726	£29,251
Ripretinib IPDE effect adjustment					
S30	Two-stage adjustment (simple covariate adjustment; log-normal distribution; STR=3.45)			£47,956	£28,209
S31	Two-stage adjustment (complex covariate adjustment; generalised gamma distribution; STR=2.72)			£48,073	£28,278
S32	Time-varying Cox proportional hazards model (treatment covariate only; HR=1.58)			£49,891	£29,347
S33	Time-varying Cox proportional hazards model (all covariates; HR=1.37)			£49,576	£29,162
S34	Open-label BID vs QD OS analysis (non-progressors + IPDE progressors; log-logistic)			£53,331	£31,371
S35	Open-label BID vs QD OS analysis (non-progressors + QD progressors; log-logistic)			£51,241	£30,142
Ripretinib IPDE cost adjustment					
S36	Cost of ripretinib 150mg BID captured in 50% of patients remaining on treatment after progression			£55,540	£32,671

S - scenario; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; DM - decision modifier; OS - overall survival; PFS - progression-free survival; TTD - time to treatment discontinuation; RPSFTM - rank-preserving structural failure time model; BSC - best supportive care; STR - survival time ratio; HR - hazard ratio; BID - twice daily; QD - once daily; IPDE - intra-patient dose escalation

* A decision modifier of 1.2 is applied in this analysis

4.3 Critical appraisal of the company's economic analysis

This section presents the EAG's critical appraisal of the company's original economic model, as described in the CS.³ Section 4.3.1 summarises the EAG's methods for the critical appraisal of the company's model. Section 4.3.2 describes the EAG's verification of the company's model. Section 4.3.3 describes the correspondence between the CS, the model inputs and their original sources. Section 4.3.4 describes the extent to which the company's economic analysis adheres to the NICE Reference Case.⁷⁷ Section 4.3.5 presents the main issues identified during the EAG's critical appraisal of the company's model.

4.3.1 Critical appraisal methods

The EAG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic analysis and the underlying model upon which this is based. These included:

- Consideration of key items contained within published economic evaluation and health economic modelling checklists.^{78, 79}
- Scrutiny and discussion of the company's model by the EAG.
- Double-programming of the deterministic version of the company's original model to fully assess the logic of the model structure, to draw out any unwritten assumptions and to identify any apparent errors in model implementation.
- Examination of the correspondence between the description of the model reported in the CS³ and the company's executable model.
- Where possible, checking parameter values used in the company's model against their original data sources.
- Replication of the base case results, PSA, DSAs and scenario analyses reported in the CS using the company's executable model.
- The use of expert clinical input to judge the credibility of the company's economic analyses and the assumptions underpinning the model.

4.3.2 Model verification by the EAG

Table 42 presents a comparison of the results of the deterministic version of the company's original model and the EAG's double-programmed model. The results obtained from the EAG's rebuilt model are similar to those generated using the company's model. However, the EAG's double-programming exercise led to the identification of several minor programming errors; these issues are discussed in detail in Section 4.3.5 (critical appraisal point 1).

Table 42: Comparison of results generated using the company's original model and the EAG's double-programmed model, includes ripretinib PAS, excludes QALY weighting, excludes correction of errors, deterministic

Option	Company's original model				EAG's double-programmed model			
	LYGs	QALYs	Costs	ICER	LYGs	QALYs	Costs	ICER
Ripretinib	3.86			-	3.86			-
BSC	0.38			-	0.38			-
Incremental	3.48			£49,021	3.48			£49,156

EAG - External Assessment Group; BSC - best supportive care; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio

4.3.3 Correspondence between the model, the CS and original sources of parameter values

Where possible, the EAG checked the company's model input values against their original sources, including the INVICTUS CSR.² The original version of the company's model included some discrepancies – in particular, the version of the life tables used in the model reflected the UK population and were outdated, the unit costs obtained from NHS Cost Collection were based on an outdated version, and the drug prices did not consistently reflect the lowest prices from eMIT. Following the clarification round, the company submitted an updated economic model. The updated model is also subject to inconsistencies in that some of the drug costs do not correspond to the least expensive versions available, and the updated general population mortality risks are based on life tables for England and Wales rather than England only.⁶¹ The EAG considers these to be minor discrepancies. The EAG notes that the NHS Cost collection online Power BI tool was unavailable for consultation after the clarification response was received, and therefore the EAG had to rely on screenshots provided by the company regarding the cost estimates that were updated at the clarification stage.⁶⁷

4.3.4 Adherence to the NICE Reference Case

Table 43 summarises the extent to which the company's economic model adheres to the NICE Reference Case.⁷⁷ The EAG does not believe that the company's model is subject to any major deviations from the Reference Case.

Table 43: Adherence to the NICE Reference Case

Element of HTA	Reference Case	EAG comments
Defining the decision problem	The scope developed by NICE	The model compares ripretinib (plus BSC) versus BSC alone. The company's economic analysis is therefore in line with the final NICE scope. ²⁰ As noted in Section 2.3.3, in TA881 ¹ the ERG's clinical advisors commented that many patients may continue to receive regorafenib following disease progression. No comparison has been presented between ripretinib versus the continued use of post-progression regorafenib. The EAG notes that sufficient data are unlikely to be available to inform an ITC.
Comparator(s)	As listed in the scope developed by NICE	
Perspective on outcomes	All health effects, whether for patients or, when relevant, carers	The model includes health outcomes accrued by patients. Health impacts on caregivers are not included.
Perspective on costs	NHS and PSS	The model includes costs borne by the NHS and PSS.
Types of economic evaluation	Cost-utility analysis with fully incremental analysis	The model is evaluated using a cost-utility approach.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The model includes a 40-year (lifetime) horizon. At the end of the time horizon, 1.5% of patients in the ripretinib group are still alive. However, this is the consequence of an error in the model (see Section 4.3.5, critical appraisal point 1).
Synthesis of evidence on health effects	Based on systematic review	Health outcomes are modelled using data collected in the INVICTUS trial. ² This is the pivotal Phase 3 trial of ripretinib for GIST. The study was identified within the company's SLR of clinical effectiveness studies.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Health state utility values are based on EQ-5D-5L data collected in INVICTUS (mapped to the 3L version). Disutilities associated with AEs have been taken from external studies, ^{62, 63, 73} none of which are based on the EQ-5D instrument.
Source of data for measurement of HRQoL	Reported directly by patients or carers, or both	
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	

Element of HTA	Reference Case	EAG comments
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit, except in specific circumstances	The CS applies a decision modifier of 1.7 which is consistent with estimates of absolute and proportional QALY shortfall generated using the York QALY Shortfall calculator. ⁷⁶
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be values using the prices relevant to the NHS and PSS	Unit costs are taken from the NHS Cost Collection, ⁶⁷ the PSSRU, ⁶⁹ the BNF ²⁶ and relevant literature. ⁶⁸
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Health outcomes and costs are discounted at a rate of 3.5% per annum.

NICE - National Institute for Health and Care Excellence; EAG - External Assessment Group; HTA - health technology assessment; ERG - Evidence Review Group; NHS - National Health Service; PSS - Personal Social Services; SLR - systematic literature review; ITC - indirect treatment comparison; QALY - quality-adjusted life year; EQ-5D - Euroqol 5-Dimensions; BNF - British National Formulary; PSSRU - Personal Social Services Research Unit; AE - adverse event

4.3.5 Main issues identified from the EAG's critical appraisal

Box 1 summarises the main issues identified within the EAG's critical appraisal of the company's economic analyses. These issues are discussed in further detail in the subsequent sections.

Box 1: Main issues identified from the EAG's critical appraisal

1. Model errors
2. Concerns regarding the exclusion of a later data-cut of INVICTUS from the model
3. Concerns regarding the company's survival analysis
4. Uncertainty around the commissioning of ripretinib 150mg BID dosing in the NHS
5. Uncertainty around the effect on ripretinib 150mg BID dosing on OS
6. Concerns relating to the modelled costs of drug wastage

(1) Model errors

The EAG's double-programming exercise identified a number of minor errors in the original version of the company's executable model:

- (a) The pain medication costs applied in the model do not reflect lowest drug prices listed in the current versions of the BNF or eMIT.^{26, 80}
- (b) The unit costs from the NHS Cost Collection⁶⁷ do not reflect the most up-to-date version.
- (c) The model uses life tables for the UK rather than England.⁶¹ The life table risks contained in the worksheet "Data Store" have not been linked to the life table risks applied as mortality constraints to the OS models.
- (d) The general population mortality constraint applied to ripretinib OS is subject to a programming error which allows the modelled risk of death for people receiving ripretinib to drop below the general population mortality risk after 285 cycles.
- (e) The CS³ (Section 3.4.4) states that the model applies AE-related QALY loss once only in the first cycle. However, the executable model applies AE-related QALY losses in every model cycle. In addition, the formulae used to calculate per-cycle AE-related QALY losses include the incorrect use of brackets which means that the QALY loss is not scaled up to the model cohort size (1,000 patients); hence, changing the cohort size changes the ICER (which should not be the case). The AE-related QALY loss is also incorrectly applied to the half-cycle corrected trace, rather than the uncorrected model trace; this means that the total expected AE-related QALY loss is not applied to patients who progress or die in the first model cycle.
- (f) The RDI estimates included in the model reflect the double-blind period of INVICTUS.² Given that the current model assumes that ripretinib treatment is permitted post-progression, the EAG believes that RDI estimates for the open-label period should be applied to post-progression ripretinib.

- (g) The costs of pre-treatment are applied using the half-cycle corrected model trace, rather than the uncorrected trace. This means that patients who progress or die during the first model cycle do not incur these costs.
- (h) The formulae which calculate the costs of palliative treatment use both the half-cycle corrected and the uncorrected trace. This introduces a minor inconsistency in the calculations.
- (i) BSC costs are included in the ripretinib group in the PF and PD (off treatment) states but are excluded from PD (on treatment) state. The EAG believes that patients who continue to receive ripretinib following disease progression would also incur BSC costs.
- (j) The model assumes that there are 52 weeks in a year; however, there are 52.18 weeks in a year.
- (k) The approach used to sample health state utility values in the PSA ignores the logical ordering of the parameters (e.g., the sampled utility value for the PD state may be lower than the sampled utility value for the PF state in the same probabilistic model run). This issue could be resolved by sampling from difference distributions using the method described by Ren *et al.*⁸¹

During the clarification round, the EAG asked the company to confirm that these issues represent errors and to provide a corrected version of the model (see clarification response,³⁵ questions B19, B20, B22, B23, B24, B25, B26, B27, B28, B29 and B33). The company's response acknowledges these issues. As part of its clarification response, the company submitted an updated model which addresses these errors. The EAG notes the following concerns regarding the updated model:

- Issue (a). Some of the pain management drug costs still did not reflect the least expensive products.
- Issue (b). The EAG was unable to check the NHS Cost Collection estimates because the Power BI tool was unavailable at the time of completion of the EAG report.
- Issue (c). The updated model uses life tables for England and Wales rather than England only.
- Issue (f). The RDI estimate from the open-label period of INVICTUS² does not appear to have been included in the updated model.
- Issue (h). The palliative treatment costs in the revised model use the half-cycle corrected trace. However, this introduces a further minor error whereby the costs for patients who progress in the first cycle are omitted from the total costs. This issue is very minor.
- Issue (j). The company's clarification response states that this issue could not be addressed due to time constraints.

The company's revised model results are summarised separately in Section 5.1.

(2) Concerns regarding the exclusion of a later data-cut of INVICTUS from the model

The data for TTD, PFS and OS used in the company's model reflect the 15th January 2021 DCO of INVICTUS.² This is the same DCO used in the economic model used to inform TA881.¹ During the clarification round for the current appraisal, the EAG asked the company to clarify whether more recent data-cuts of INVICTUS are available, and if so, why these had not been used in the model (see clarification response,³⁵ question B1). The company's response states that there is a later DCO from INVICTUS from May 2022, but these data have not been included in the model. This later DCO would have provided approximately 16 months of additional follow-up compared with the January 2021 DCO. The company's clarification response includes additional clinical data from the May 2022 DCO on patient disposition, Kaplan-Meier plots for OS and an updated HR for OS (excluding adjustment for treatment switching onto ripretinib in the placebo group).

The company's clarification response³⁵ states that preparation and analysis for the CS for the current appraisal³ began before the 2022 DCO analysis of INVICTUS became available. The clarification response also highlights that the HRs for OS for ripretinib versus placebo are similar between the January 2021 and May 2022 DCOs (0.41 versus [REDACTED], respectively). Despite this, the company states that it considers the May 2022 DCO to be less robust than the earlier January 2021 DCO, noting that the pre-specified end-of-study analysis included OS and safety, but not PFS or HRQoL; as such, incorporating the May 2022 data would result in different DCOs being applied between the clinical end points used in the model. The company's response also argues that the 2022 DCO would increase the risk of bias and confounding in the OS data due to a greater reliance on data collection during the open-label period of INVICTUS.³⁵

The EAG acknowledges that incorporating the later DCO into the economic model would require all of the company's analyses of OS from INVICTUS² to be repeated, including the statistical adjustment of OS to account for treatment switching in the placebo group, the statistical adjustment of OS to account for IPDE to 150mg ripretinib BID dosing (applied in the company's scenario analyses only) and updating the parametric survival models fitted to the adjusted OS data. However, the EAG believes that the company should have applied the latest DCO for OS, with appropriate statistical adjustments, as this would have provided additional information to inform long-term predictions of OS. Figure 32 presents overlaid Kaplan-Meier plots of ripretinib OS from the 2021 and 2022 DCOs; OS data for the placebo group are not presented here as they were not adjusted for treatment switching.

The EAG considers that, despite the limitations of follow-up during the unblinded period, long-term follow-up data would provide valuable insights. In particular, such data could help clarify the trajectory of longer-term HRs and hazard shapes, both of which are important considerations for survival

extrapolation. Specifically, an additional year of follow-up would better characterise the tail of the survival distribution which could help to inform parametric survival model selection.

Intercurrent events such as IPDE in the experimental arm and treatment crossover in the control arm complicate interpretation of the ITT analysis. However, the company has attempted to address these issues using the two-stage adjustment method (Section 4.2.4), which the EAG deems reasonable. With longer follow-up, more patients are expected to progress, increasing the effective sample size for both IPDE and crossover adjustments. This would likely allow for more reliable estimates, provided potential biases are appropriately accounted for through the chosen covariates – which the EAG’s clinical advisors considered reasonable – and characterisation of longer-term treatment effects. In line with TSD 24,⁴⁷ which recommends presenting two-stage adjustment results both with and without re-censoring, longer-term data would be especially valuable to mitigate information loss in the re-censoring scenarios (i.e., EAG’s preferred scenarios for addressing treatment switching in the control arm and IPDE in the ripretinib arm).

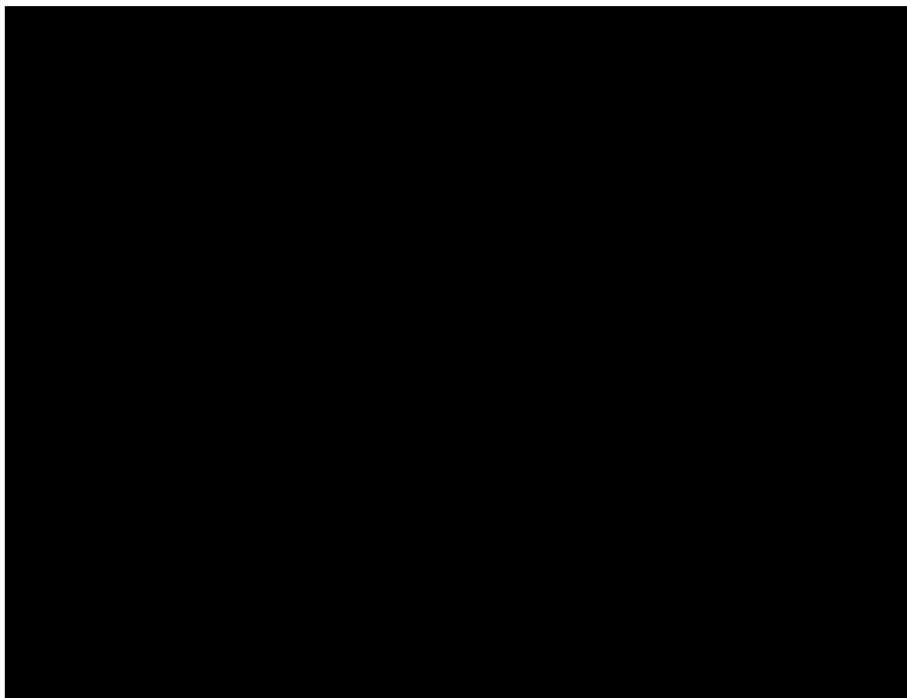
Although outcome measurement could be affected by the open-label nature of the follow-up data, the EAG notes that OS is a hard endpoint and therefore less susceptible to subjective influences. While the company stated concerns regarding the open-label nature of the data at the FAC stage of the appraisal, the EAG’s considers that the benefits of examining longer-term follow-up outweigh the risks. Excluding these data would constrain the understanding of longer-term survival outcomes and may increase decision uncertainty. Given the absence of alternative evidence on longer-term ripretinib use, the EAG considered that including the long-term data would have provided a more balanced basis for decision-making.

Figure 32: Overlaid Kaplan-Meier plots for OS from the January 2021 and the May 2022 DCOs, ripretinib group (data digitised by the EAG)

OS - overall survival; DCO - data cut-off

(3) Concerns regarding the company’s survival analysis

The EAG has several concerns regarding the parametric survival modelling presented in the CS.³ These concerns are discussed below in terms of the general considerations around model fitting and selection set out in NICE DSU TSDs 14 and 21.^{82, 83}



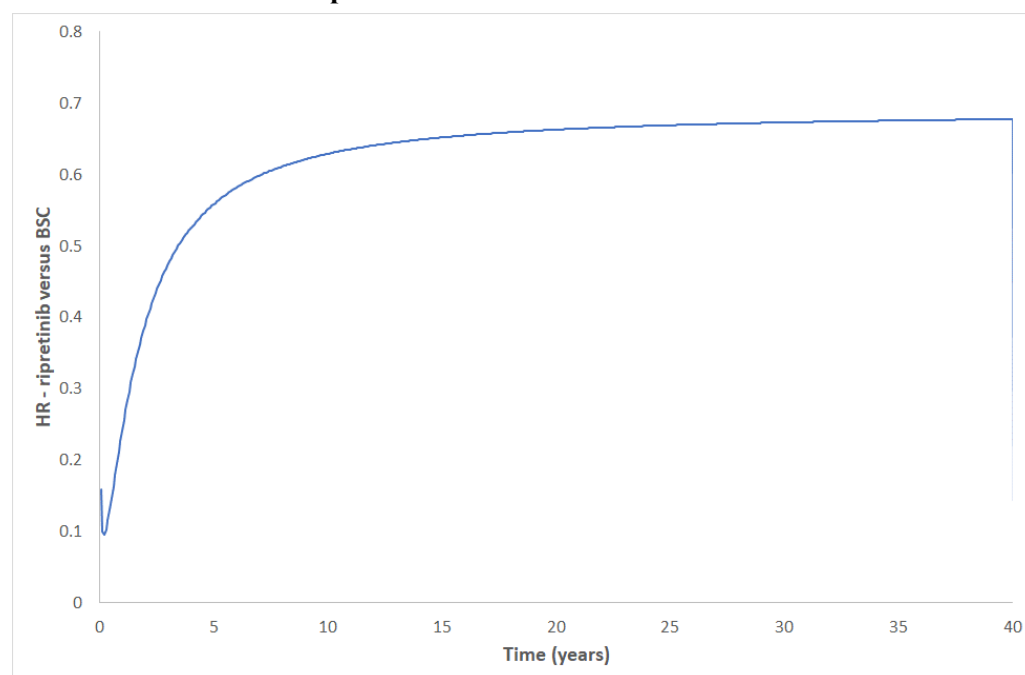
(a) Use of independent models fitted to data for each treatment group

The company considered the potential for jointly fitted models for PFS and OS through consideration of log cumulative hazard plots, plots of Schoenfeld residuals and global Schoenfeld residuals tests. For PFS, the CS³ states that the log-cumulative hazards were not strictly parallel, the Schoenfeld residuals plot suggests that the HR is likely to vary over time and the global Schoenfeld test suggested a p -value which was less than 0.05. This indicates that the PH assumption may not hold. For OS, the CS states that the log-cumulative hazard plot and Schoenfeld residuals plot suggest that applying the PH assumption would be reasonable and the global Schoenfeld test suggests that the PH assumption cannot be ruled out ($p > 0.05$). However, the company instead elected to fit separate parametric survival models to the OS data for each treatment group (including the statistical adjustment of the OS data to account for confounding due to switching in the placebo group).

The EAG notes that the plots and tests undertaken by the company relate specifically to the assessment of PH models (the exponential, Weibull and Gompertz distributions). AFT models do not make the PH assumption; the appropriateness of using jointly fitted AFT models instead requires consideration of Q-Q plots, which have not been presented in the CS.³ In general, the EAG prefers to avoid models which apply a constant HR or acceleration factor (AF), as this usually reflects an unnecessary and restrictive modelling assumption. As such, the EAG agrees with the company's decision to fit independent models to the data for each treatment group. However, the EAG also notes that whilst a constant lifetime treatment effect parameter (e.g., an HR or AF) is not used in the economic model, it is important to consider what is implicitly being assumed about relative treatment effects for ripretinib versus BSC. Figure 33 shows that the independent log-logistic OS models implicitly suggest a time-varying HR for OS which favours ripretinib over BSC at all timepoints (i.e., the HR is consistently < 1.0). In TA881,¹ one of the EAG's clinical advisors commented that they would not expect a residual treatment effect on OS in patients after they have discontinued ripretinib. The company's model predicts that virtually all patients will have discontinued ripretinib by 5 years; hence, the time-varying HR implied by the

company's OS model selection appears to reflect an optimistic scenario. However, the implied treatment effect is subject to uncertainty as the model predicts that almost all BSC-treated patients will have died within 2 years.

Figure 33: Time-varying HR for OS implied by independent log-logistic models used in the company's base case analysis, generated by the EAG using the company's corrected post-clarification version of the model*



BSC - best supportive care

* HR calculated from approximate hazard for in each group. Plot excludes general population survival constraint

(b) Range of models assessed

The company fitted six standard parametric survival models to the available data on PFS and OS (see Figure 22, Figure 23, Figure 26 and Figure 27) and eight standard parametric survival models to the data on TTD+PFS (see Figure 19). Other more flexible survival distributions, e.g., RCS models, were not considered. The EAG notes that based on visual assessment alone, some of the fitted standard parametric survival models appear to provide a good fit to the PFS data in both groups. However, the overall visual fit of the models to the ripretinib OS data is poor, and the Kaplan-Meier functions suggest that there are potential turning points in the underlying hazard function which are not fully captured by the standard models. The use of more flexible parametric models may have been better able to reflect the observed ripretinib OS data.

(c) Statistical and visual goodness-of-fit

The EAG notes the following observations regarding the fitted parametric survival models:

- *TTD+PFS (see Figure 19 and Table 26):* The log-logistic model has the lowest AIC and BIC values. The company selected the exponential distribution for inclusion in the economic model. All of the models appear to slightly underestimate TTD in the first 12 months. The log-logistic

and log-normal distributions have longer tails compared with the other models, indicating longer time on treatment.

- *PFS (see Figure 22, Figure 23 and Table 27)*: The log-logistic model has the lowest combined AIC and BIC values across both treatment groups. The log-normal model provides similar combined AIC and BIC values, and the generalised gamma model provides a similar fit in terms of combined AIC, but not BIC. The company selected the log-normal distribution for inclusion in the economic model. All six fitted models appear to give similar projections for the BSC group, with virtually all patients having progressed or died within 12 months. With respect to the ripretinib group, the log-logistic and log-normal models have longer tails and provide more optimistic extrapolations compared with the other candidate models. These two models both appear to overestimate PFS compared with the observed data after around 1.5 years.
- *OS (see Figure 26, Figure 27, and Table 28)*. The log-logistic model has the lowest combined AIC and BIC values. The log-normal model provides a similar fit in terms of combined AIC and BIC, whilst the exponential model has a similar combined BIC. The company selected the log-logistic distribution for inclusion in the economic model. Visually, all models provide broadly similar projections of OS for the BSC group, with very few patients surviving beyond 2 years. Within the ripretinib group, the models fall into two clusters, with the log-logistic, log-normal, Gompertz and generalised gamma models providing markedly more optimistic OS extrapolations than the Weibull and exponential models. All of the models for the ripretinib group appear to overestimate OS relative to the observed data after around one year.

(d) Consideration of nature of hazards

Modelled hazard plots for TTD are presented in CS Appendix J;²⁹ neither the CS³ nor its appendices present empirical or modelled hazard plots for OS or PFS. However, plots of the unsmoothed and smoothed empirical hazards and the modelled hazards for PFS and OS were provided as part of the company's response to clarification questions in TA881;¹ these plots have been reproduced in Figure 20, Figure 21, Figure 24 and Figure 25. These plots can be useful for assessing whether the hazard functions for the selected models are consistent with the underlying hazards in the observed data.

With respect to these hazard plots, the EAG makes the following observations:

- *TTD+PFS (see Figure 18)*: The smoothed empirical hazard for TTD+PFS increases until around 35 weeks (8 months) and then decreases beyond this time point. The company's selected exponential TTD model assumes a constant hazard and is therefore inconsistent with the observed hazard. The generalised F, generalised gamma, log-normal and log-logistic distributions may better reflect the pattern in the observed hazard.
- *PFS (see Figure 20 and Figure 21)*: The smoothed empirical hazard for PFS in both treatment groups appears to increase, decrease and then increase again. The log-normal distribution, which was selected for inclusion in the company's base case analysis, assumes that the hazard

increases and then decreases. The company's clarification response in TA881¹ noted that only 8 patients in the placebo group remain at risk after 8 weeks; hence, the plot should be interpreted with caution. Notwithstanding this uncertainty, the modelled hazard for the log-normal distribution appears to be inconsistent with the empirical hazard for PFS in both groups. However, none of the fitted parametric survival models reflect this underlying pattern because, at most, these models can capture one turning point. It is possible that more flexible parametric models could have better reflected the empirical hazards.

- *OS (see Figure 24 and Figure 25):* The smoothed empirical hazard for OS in both treatment groups increases and then decreases. This is generally consistent with the underlying assumptions of the log-logistic model which was selected for inclusion in the company's base case analysis. However, the EAG notes that the empirical hazard in both groups decreases more rapidly than the predicted hazards from the company's log-logistic models.

(e) Consideration of long-term clinical plausibility

In TA881,¹ the ERG criticised the company's model selection process because it appeared to have been based only on goodness of fit and did not explicitly include consideration of the clinical plausibility of the alternative survival distributions. The CS for the current appraisal³ provides some, albeit limited, discussion regarding considerations of the clinical plausibility, stating that the log-logistic model for ripretinib provides a 10-year OS probability which is consistent with the upper end of the clinical experts' estimates of OS at the company's July 2024 advisory board meeting. The minutes of the 2022 and 2024 advisory board meetings held by the company^{27, 40} include further details of the clinical experts' views regarding potentially plausible models for OS. The OS models preferred by the company and the clinical experts who attended these meetings are summarised in Table 44, together with details of the final models selected for inclusion in the CS. As indicated in the table, the views regarding the most appropriate OS model varied between the company and the clinical experts across the meetings, with the log-normal, generalised gamma and exponential models each being preferred by the experts and/or the company. The company's base case analysis for the current appraisal includes the log-logistic OS distribution which does not appear to have been preferred by the clinical experts at either the 2022 or 2024 advisory board meetings. Of particular note, the log-logistic OS model suggests that ■■■ of patients receiving ripretinib will remain alive at 10 years. The minutes of the 2024 advisory board meeting⁴⁰ state that: ■■■

■■■

■■■

■■■ The EAG notes that the costs of future effective subsequent-line treatments are not included in the company's economic model and therefore the effects of such treatments on OS should not be considered a relevant factor in model selection. The company's clarification response³⁵ (question B10) provides some further detail regarding the views of the clinical

advisors at the 2024 advisory board meeting. Amongst the seven clinical advisors who attended the meeting, one advisor considered ■ survival at 10-years to be plausible (as described above), one commented that ■ OS at 10 years was an overestimate and following the meeting, four clinical advisors provided estimates of 10-year OS for ripretinib of ■, all of which are lower than the predicted OS from the log-logistic model selected by the company. Clinicians' estimates of expected OS at 10 years were not reported in the minutes of the 2022 advisory board meeting. Based on the advisory board meeting minutes and the company's clarification response, the company has selected a base case OS distribution which produces substantially more optimistic predictions of OS than the expected OS estimates suggested by most of the clinical experts who attended the 2024 advisory board meeting.

Despite the consensus view from clinicians that the log-logistic model overestimates ripretinib OS, the company's clarification response³⁵ states that *"Previous NICE TAs for advanced GIST indicate that clinicians repeatedly underestimate long term survival associated with TKI treatment."* In support of this argument, the company's response highlights that observational studies of first-line imatinib have indicated a PFS probability of nearly 10% at 10 years^{53, 84} and an observational study of second-line sunitinib has shown an OS probability of around 10% at 10 years,⁸⁵ despite lower expectations of long-term OS being provided by clinical experts during the NICE TAs of these treatments.^{46, 86} One of the EAG's clinical advisors commented that clinical expectations of OS during these earlier appraisals would not have accounted for the effects of other subsequent-line therapies which were not available at the time. The company's clarification response also highlights that the ORR, median PFS and median OS for ripretinib in INVICTUS² are higher than estimates reported from pivotal trials of sunitinib and regorafenib, despite ripretinib being used in more heavily pre-treated patients who are more likely to harbour secondary drug-resistance mutations. The clarification response goes on to state that on the basis of the real-world estimates of OS for treatments used at earlier treatment lines, the greater benefit of ripretinib versus other TKIs, and uncertainty surrounding clinicians' predicted OS, the company decided that a 10-year OS probability of ■ was *"too low"* and the estimate of ■ based on the log-logistic model is plausible.

Table 44: Summary of preferences for alternative OS models from company's advisory board meeting minutes and the CS

Document	Preferred OS model	Basis for preference	EAG comments
2022 advisory board meeting ²⁷	<i>Company:</i> Log-normal	Based on model fit.	The clinical experts recommended challenging the ERG's preferred two-stage adjusted generalised gamma model because it does not take into account the effect of post-progression treatment (EAG note: the company's model in TA881 ³ assumed that all patients discontinue ripretinib at the point of disease progression, therefore post-progression effects on OS should not be considered in the model).
2024 advisory board meeting ⁴⁰	<i>Company:</i> Generalised gamma <i>Clinical experts:</i> Exponential	Based on AIC (EAG note: EAG note: the generalised gamma model has the fourth lowest combined AIC value). Based on a view that hazard of death is static for the majority of patients.	Some clinical experts agreed that risk increases initially, plateaus, decreases and then increases. The minutes of the advisory board meeting state that: [REDACTED] [REDACTED] (EAG note: the costs of future effective treatments are not included in the economic model).
2025 advisory board meeting ⁴¹	The plausibility of parametric survival models was not discussed during this meeting		
CS (2025) ³	<i>Company:</i> Log-logistic	The log-logistic model has lowest combined AIC and BIC. The 10-year predicted OS of [REDACTED] from the log-logistic model is in line with upper estimate of survival from 2024 advisory board meeting. Clinicians agreed that the log-logistic model hazard would reflect reality.	All other ripretinib OS models are explored in scenario analyses (see Table 41). Hazard plots are not presented in the CS but were included in the company's clarification response in TA881 (see Figure 24).

OS - overall survival; CS - company's submission; AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; ERG - Evidence Review Group; EAG - External Assessment Group

The EAG asked their clinical advisors for their views regarding the plausibility of the company's model predictions of TTD, PFS and OS. Their views are summarised below.

TTD

- One of the EAG's clinical advisors considered either the exponential or generalised gamma distributions to be potentially appropriate. The EAG was unable to obtain the view of the second clinical advisor regarding the TTD function.

PFS

- One of the EAG's clinical advisors considered the company's predictions of PFS based on the log-normal distributions (the yellow lines in Figure 22 and Figure 23) to be plausible for both treatment groups. The other clinical advisor preferred the generalised gamma model for ripretinib PFS and the Weibull model for BSC PFS. Both clinical advisors agreed that it was plausible that all patients receiving BSC would progress within one year and that a small proportion of patients receiving ripretinib could derive a long-term benefit in PFS.

OS

- Both of the EAG's clinical advisors commented that they believed that continuing ripretinib beyond disease progression would lead to additional OS benefits. Both advisors also stated that they would expect ripretinib 150mg BID dosing to lead to some improvement in OS relative to 150mg QD dosing, although the magnitude of such benefit is unclear from the available INVICTUS data.²
- The EAG's first clinical advisor stated that in the 4L+ setting, it is likely that nearly all BSC-treated patients will have died within 1.5 years. They commented that for the BSC group, the log-normal and log-logistic distributions appear to be overly optimistic, whereas the Weibull and Gompertz distributions appear to be overly pessimistic. They considered the generalised gamma model to be the most plausible distribution. With respect to the ripretinib group, the clinical advisor considered that a predicted 10-year OS probability of [REDACTED] was "*too optimistic*", even in the situation in which ripretinib is used post-progression. The clinical advisor instead considered the Weibull and exponential models to be more clinically plausible; these models suggest 10-year OS probabilities of [REDACTED] and [REDACTED], respectively.
- The EAG's second clinical advisor considered that the Weibull and generalised gamma models provide the most plausible predictions of BSC OS, and the exponential and Weibull models provide the most plausible predictions of ripretinib OS, including the effects of post-progression treatment.
- Overall, the EAG considers that the company's selected log-logistic model generates predictions of long-term OS for ripretinib which appear to be highly optimistic, as indicated by the EAG's clinical advisors and the majority of clinical advisors who attended the company's 2024 advisory board meeting.⁴⁰

(f) Sensitivity analysis

The CS³ presents the results of a comprehensive range of scenario analyses which consider the use of all alternative parametric survival models for TTD, PFS and OS (see Table 41, Scenarios S4-S18). These analyses indicate that the ICER for ripretinib versus BSC is particularly sensitive to the selected model for OS.

EAG's conclusions regarding company's survival modelling

Overall, the EAG considers the company's survival modelling to be limited, in particular due to: (i) the poor visual fit of the fitted models to the ripretinib OS data; (ii) the implicit assumption of a lifetime treatment effect on OS and (iii) the selection of the log-logistic model for the ripretinib group which produces predictions of OS which were considered to be implausibly optimistic by the EAG's clinical advisors and which are higher than estimates of expected 10-year OS provided by most of the clinical experts consulted at the company's 2024 advisory board meeting.

The EAG's preferred models are summarised in Table 45. These survival models are applied in the EAG's preferred analysis; all other models are considered in the EAG's additional sensitivity analyses (see Section 5.2).

Table 45: Summary of EAG's preferred parametric survival models

End point	Company's selected model	EAG's preferred model	Justification for EAG preferred model selection and additional comments
TTD	Exponential	Exponential	Based on EAG and company's experts' preferences. Modelled hazard does not reflect shape of empirical hazard.
PFS ripretinib	Log-normal	Log-normal	Best-fitting model which is generally consistent with shape of empirical hazard function. Log-normal model preferred by EAG in TA881.
OS ripretinib	Log-logistic	Exponential (unadjusted OS data) Log-logistic (when OS is adjusted for BID dosing)	Based on EAG clinician preferences. Model prediction of 10-year OS is closest to the overall estimate of █████ suggested by company's advisors. Modelled hazard does not reflect shape of empirical hazard. When OS is adjusted for the effects of BID dosing, the EAG prefers the log-logistic model.
PFS BSC	Log-normal	Log-normal	Best-fitting model which is generally consistent with shape of empirical hazard function. Log-normal model preferred by EAG in TA881.
OS BSC	Log-logistic	Generalised gamma	Based on EAG clinician preferences. Generalised gamma model preferred by EAG in TA881. The EAG notes that this is a different distribution compared with that selected as EAG's preferred model for the ripretinib group.

EAG - External Assessment Group; TTD - time to treatment discontinuation; PFS - progression-free survival; OS - overall survival; BSC - best supportive care

(4) Uncertainty around the commissioning of ripretinib 150mg BID dosing in the NHS

The company's base case model uses the unadjusted OS data for the ripretinib arm of INVICTUS² and applies only the costs of ripretinib 150mg QD. Taken together, this assumes that the same OS outcomes observed in the ripretinib arm of INVICTUS (including the effects of post-progression 150mg BID dosing in some patients) can be achieved by using less of the drug (i.e., using QD dosing in all patients). The clinical advisors who attended the company's 2024 advisory board meeting⁴⁰ agreed that dose escalation to ripretinib BID in the trial will have had a "*non-negligible effect*" on OS. The EAG's clinical advisors stated that they would expect BID dosing to improve OS, but they considered the magnitude of the benefit to be uncertain. The EAG's clinical advisors also commented that they would dose-escalate to ripretinib 150mg BID for patients who are able to tolerate this higher dose if they were permitted to do so. Therefore, the EAG has concerns that the company's base case model introduces an inconsistency between the health outcomes observed in the trial and the costs required to generate those health outcomes. Whilst the company's base case analysis excludes any explicit consideration of the costs or effects of BID dosing, the CS³ reports the results of six scenario analyses which attempt to adjust OS to account for the effects of BID dosing (see Table 41, Scenarios S30-35), as well as an additional scenario analysis in which the costs of BID dosing are included for 50% of patients' post-progression ripretinib treatment time (see Table 41, Scenario S36). Most of the IPDE adjustment analyses presented in the CS have a relatively small impact on the ICER; however, the ICER for Scenario S36 is around £4,000 higher than the company's base case estimate. As noted in Section 4.2.4, additional two-stage estimation analyses were conducted as part of the company's response to clarification question B9;³⁵ however, ICERs were not provided in the company's response document.

During the clarification process, the EAG asked the company to calculate the proportion of post-progression ripretinib exposure time in INVICTUS² that patients spent receiving the BID dose and to explain why Scenario S36 (which includes the costs of BID dosing) was not applied in the company's base case (see clarification response,³⁵ questions B16 and B12, respectively). The company's response states that 60.1% of post-progression ripretinib exposure time was spent receiving BID dosing; this estimate is 10.1% higher than the proportion applied in Scenario S36. The company's clarification response also states that the costs of BID dosing are not included in the base case model because: (i) the ripretinib 150mg BID dose reflects an off-licence use of the drug and that NICE can only issue guidance within the marketing authorisation for a given health technology, and (ii) the company is unclear how BID dosing would be commissioned in the NHS and whether off-licence use would be a barrier to the use of the higher dose. The company's clarification response states that it has sought clarity from NHS England about whether BID dosing would be commissioned in the NHS but has not yet received a response. It also states that if BID dosing was commissioned by individual funding requests, "*its use in clinical practice is likely to be far lower than that captured in the model scenario*" (50%). The company argues that there is too much uncertainty for Scenario S36 to be considered in the base case analysis.

The EAG believes that this uncertainty can only be resolved by obtaining further input from NHS England regarding how ripretinib would be commissioned in the NHS. However, regardless of whether BID dosing would be routinely commissioned in practice, the EAG believes that the company's base case model either underestimates the incremental costs or overestimates the incremental benefits of ripretinib:

- (i) If BID dosing is not routinely commissioned by NHS England, the EAG's preferred analysis would be to apply the OS data from the ripretinib arm of INVICTUS² including adjustment to account for BID dosing using the 2-stage method and to apply the costs of QD dosing to 100% of the total post-progression ripretinib treatment time. This approach would reflect the OS outcomes and costs associated with QD dosing only.
- (ii) If BID dosing is routinely commissioned by NHS England, the EAG's preferred analysis would be to apply the OS data from the ripretinib arm of INVICTUS² without adjustment for BID dosing and to include the costs of BID dosing for 60.1% of the total post-progression ripretinib treatment time. This approach would reflect the OS outcomes and costs associated with the combination of BID and QD dosing seen in the trial.

The EAG's exploratory analyses include scenarios which attempt to align health outcomes and costs in both of these commissioning situations (see Section 5.2, EAG's preferred analysis "EA4" and sensitivity analysis "ASA1").

(5) Uncertainty around the effect on ripretinib 150mg BID dosing on OS

As detailed in Section 4.2.4, the company explored six scenario analyses across three methodological approaches to evaluate the impact of IPDE on OS:

- Censored BID analyses (two scenarios: "open-label BID vs QD OS analysis [non-progressors + IPDE]" and "open-label BID vs QD OS analysis [non-progressors + QD]")
- Time-varying Cox models (two scenarios: treatment covariate only model; all covariates model)
- Two-stage adjustments (two scenarios: simple model; complex model).

Because the censored BID analyses selected patients based on post-randomisation characteristics, they are subject to selection bias and therefore cannot provide a causal estimate of the effect of IPDE on OS. It should also be noted that the "open-label BID vs QD OS analysis (non-progressors + IPDE)" analyses attempted to isolate the effect of BID dosing, rather than estimating OS had patients remained on QD dosing after progression (i.e., this is different from the other five IPDE scenario analyses).

The scenario analyses using time-varying Cox models, including one with only IPDE as a covariate and a more complex model incorporating all covariates, also had methodological limitations. Specifically, simply including time-varying covariates in a Cox regression model does not adequately address time-

varying confounding, as causal methods such as marginal structural models were not applied. As a result, the models yielded counterintuitive estimates suggesting that BID dosing was harmful, which contrasts with clinical expectations.

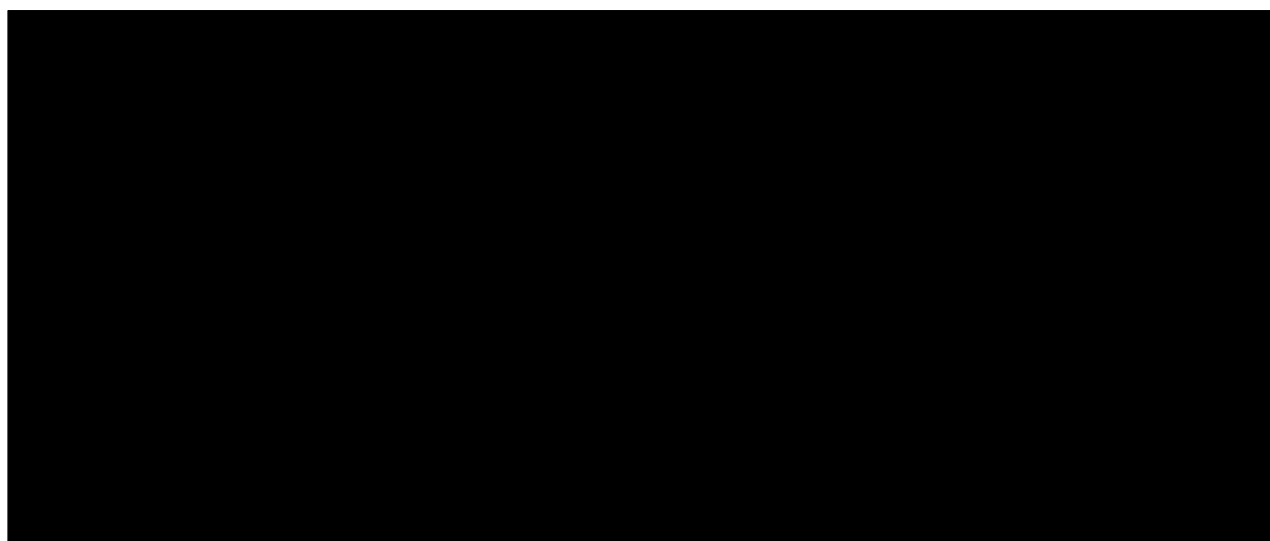
The EAG considers the two-stage adjustment approach to be the most appropriate, in line with TSDs 16 and 24.^{48, 70} Due to the small sample size, the company did not conduct IPCW adjusted analysis as an alternative approach, which the EAG considers to be reasonable.

Although the two-stage adjustment reported in the CS³ incorrectly implemented the time ratio in the economic model, the EAG considers the company's corrected analysis provided in response to clarification question B9³⁵ to be appropriate. Nonetheless, considerable uncertainty remains and this is discussed below.

Six distributions were used to derive time ratios, each applied with and without re-censoring. Six parametric survival models for survival extrapolation were then fitted to each counterfactual OS dataset, resulting in a total of 144 scenarios. In all scenarios, the time ratios exceeded 1.0, suggesting a beneficial effect of IPDE on OS. In the original CS,³ the company selected one simple model (using the log-normal distribution) and one complex model (using the generalised gamma distribution) to derive time ratios. In the updated analysis provided as part of the company's clarification response to question B9,³⁵ the company considered the simple model using the log-normal distribution with re-censoring as the preferred method for deriving counterfactual OS. However, no clear specification was provided regarding the preferred parametric model for the extrapolation of the adjusted survival data. Despite the updated ICERs not being presented in the company's response, the updated executable model includes additional functionality which allowed the EAG to explore the ICERs associated with each of these scenarios.

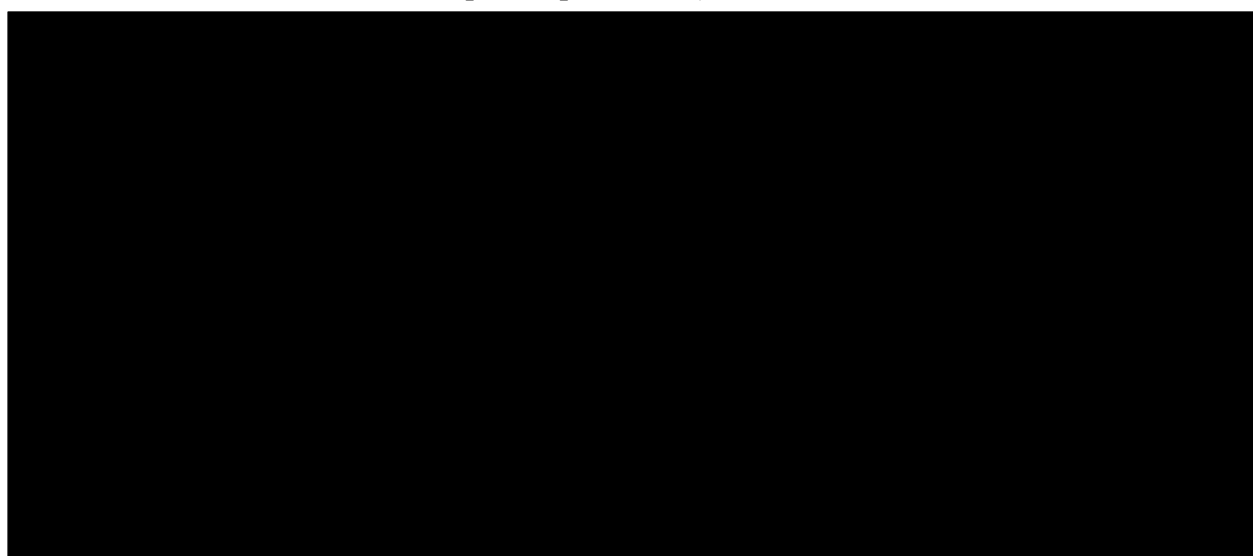
In contrast to the company's preference, the EAG favours the complex model using the generalised gamma distribution to derive the time ratio, as it had the lowest AIC among all models assessed. Since these distributions were not used for survival extrapolation, statistical fit alone was sufficient for selection. However, this still led to 12 survival extrapolations to consider: counterfactual OS (using complex generalised gamma distribution) with and without re-censoring, with six potentially plausible parametric models fitted to the adjusted data. Among these 12 scenarios, the EAG prefers the log-logistic model with re-censoring for extrapolation (Figure 34 shows OS from six parametric models fitted to the counterfactual OS with re-censoring using the generalised gamma model). This model's hazard function closely aligned with the smoothed empirical hazard (see Figure 35), and the extrapolation projected a 10-year survival that was similar to, but slightly lower than, the EAG's preferred extrapolated unadjusted OS model (Figure 36).

Figure 34: Kaplan-Meier plot of unadjusted OS and OS adjusted for BID dosing using the two-stage method, complex, generalised gamma model, with re-censoring (reproduced from clarification response, question B9)



AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; Gen - generalised; LL - log-likelihood.

Figure 35: Observed and modelled hazards of OS adjusted for BID dosing using the two-stage method, complex, generalised gamma model, with re-censoring (reproduced from clarification response, question B9)



AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; Gen - generalised; LL - log-likelihood.

The EAG notes the importance of presenting the results with and without re-censoring. While re-censoring helps to reduce bias by breaking the dependency between treatment switching, censoring, and patient prognosis, thereby supporting the validity of estimated treatment effects, it comes at the cost of the loss of some longer-term data, and the extent of data loss increases with the magnitude of the estimated treatment effect (i.e., time ratios), introducing uncertainty into extrapolations.

Therefore, in line with TSD 24,⁷⁰ the EAG prefers to present results both with and without re-censoring to support a balanced interpretation, as each approach may introduce bias in different directions and

thus uncertainty remains. The EAG notes that the re-censoring scenario with the complex generalised gamma model for time ratio estimation and the log-logistic model for survival extrapolation generates a predicted probability of 10-year OS consistent with estimates provided by the EAG's clinical advisors and most of the clinical advisors consulted by the company. The without re-censoring scenario generates a higher predicted probability of 10-year OS for all six parametric survival models compared to the equivalent models including re-censoring. Since the counterfactual OS curve based on the complex generalised gamma model may differ when re-censoring is excluded, the log-logistic model may no longer be the most clinically plausible option for survival extrapolation in that context. Model results for the complex generalised gamma model with and without re-censoring are included in the EAG's additional sensitivity analyses (see Section 5.2.4).

In summary, considerable uncertainty remains around the IPDE-adjusted OS scenarios. Additionally, the counterfactual OS estimates were based on point estimates of the time ratio. Although bootstrapping could offer a more comprehensive way to account for residual uncertainty, the EAG acknowledges that there are currently no readily available open-source tools to support such an implementation.

(6) Concerns relating to the modelled costs of drug wastage

In TA881,¹ the company's original model did not include any drug wastage; the ERG's preferred model assumed that one-quarter of a pack of ripretinib would be wasted per patient initiating treatment. The Appraisal Committee concluded that it was appropriate to include drug wastage in the model, and that the ERG's estimate of 0.25 packs wasted per person was plausible. The company's approach to modelling drug wastage for ripretinib in the current appraisal³ is based on an integer pack-based approach. This approach tracks whether a new pack of 90 ripretinib tablets is required in each 28-day model cycle (including RDI adjustment), with a new pack being required in 9 of every 10 cycles. This pack-based approach leads to an estimate of 47% of a pack of ripretinib being wasted over a patient's lifetime. This estimate is higher than the estimate previously accepted by the Appraisal Committee in TA881. The EAG is unsure why the company adopted the pack-based approach. Following the clarification round, the company amended its model to instead assume that 25% of a pack is wasted per patient initiating treatment with ripretinib (see clarification response,³⁵ question B25).

5. COMPANY'S UPDATED MODEL RESULTS AND EAG'S EXPLORATORY ANALYSES

This chapter presents the results of the company's updated economic model and the methods and results of the EAG's exploratory analyses. Section 5.1 presents the results of the company's updated model. Section 5.2 presents the methods and results of the EAG's exploratory analyses. Section 5.3 presents a brief discussion around decision modifiers which are relevant to this appraisal. Section 5.4 summarises the conclusions of the economic analyses presented by the company and the EAG.

5.1 Company's updated cost-effectiveness results, post-clarification model

5.1.1 Company's updated base case results

Table 40 presents the central estimates of cost-effectiveness generated using the updated model which was submitted as part of the company's clarification response³⁵ (previously described in Section 4.3.5, critical appraisal point 1). The results presented in the table include the proposed PAS for ripretinib and a decision modifier of 1.7. The probabilistic version of the model suggests that ripretinib is expected to generate an additional [REDACTED] discounted QALYs at an additional cost of [REDACTED]. Including a decision modifier of 1.7, the corresponding ICER is £28,576 per QALY gained. The deterministic version of the model results in a slightly higher ICER of £28,730 per QALY gained. These ICERs are slightly lower than those presented in the CS.³

Table 46: Company's updated base case results, ripretinib versus BSC, post-clarification model (generated by the EAG using the company's updated model)

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER (excl. DM)	ICER (incl. DM)
Probabilistic model[†]								
Ripretinib	NR	[REDACTED]	[REDACTED]	NR	[REDACTED]	[REDACTED]	£48,578	£28,576
BSC	NR	[REDACTED]	[REDACTED]	-	-	-	-	-
Deterministic model								
Ripretinib	3.06	[REDACTED]	[REDACTED]	2.69	[REDACTED]	[REDACTED]	£48,842	£28,730
BSC	0.37	[REDACTED]	[REDACTED]	-	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; DM - decision modifier; BSC - best supportive care; NR - not reported

[†] The company's updated model includes an error in the probabilistic sampling sub-routine which allows sampled probabilities of TTD to be >1.0 when either the exponential or Gompertz distributions are selected. The results shown here include a correction to the exponential distribution for TTD whereby the log mean of the rate parameter is sampled and then exponentiated back onto the natural scale.

5.1.2 Scenario analyses conducted by the company using the updated model

The company's clarification response³⁵ presents the results of a selected set of scenario analyses using the updated model which address specific issues highlighted in the EAG's clarification letter. These analyses included scenarios relating to: the inclusion of costs associated with the proportion of total post-progression time spent receiving ripretinib 150mg BID; the inclusion of AE frequencies from the

open-label period of INVICTUS;² the inclusion of BSC costs based on INVICTUS; the inclusion of pack-based wastage and the inclusion of alternative end-of-life care costs based on Round *et al.*⁷⁵ The results of these analyses are shown in Table 47. None of these selected scenarios have a substantial impact on the model results. The highest ICER relates to the scenario which includes the costs of ripretinib 150mg BID dosing applied to 50% of the post-progression survival time (this analysis was also presented in the company's original scenario analyses; see Table 41, Scenario S36). The results of the other scenario analyses presented in the CS³ (reproduced in Table 41) were not repeated in the company's clarification response.

Table 47: Results of selected scenario analyses presented in the company's clarification response (generated by the EAG using the company's updated model)

Scenario	Incremental QALYs	Incremental cost	ICER excluding DM	ICER including DM
Company's updated base case model (deterministic)			£48,842	£28,730
Assume 50% BID use in the PDOn state (clarification question B12)			£55,496	£32,645
AEs based on double-blind period only (clarification question B15)			£48,873	£28,749
BSC costs based on INVICTUS BSC arm (clarification question B17)			£49,112	£28,889
Apply integer pack-based wastage calculations (clarification question B25)			£50,442	£29,672
End-of-life care costs from Round <i>et al.</i> ⁷⁵ (clarification question B32)			£49,011	£28,830

EAG - External Assessment Group; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; DM - decision modifier; BID - twice daily; PDOn - progressed disease on treatment; AE - adverse event; BSC - best supportive care

5.2 EAG exploratory analysis

5.2.1 EAG exploratory analysis - methods

The EAG undertook exploratory analyses (EAs) using the updated version of the model which was provided as part of the company's clarification response.³⁵ All analyses were undertaken by one modeller and checked by a second modeller. All analyses presented in this section reflect the PAS price of ripretinib. Results are presented with and without QALY weighting (decision modifier = 1.7).

5.2.2 EAG's preferred analysis

The EAG's preferred analysis is comprised of 3 sets of amendments to the company's updated model. EA1 includes the correction of errors; EA2 and EA3 are conducted independently but include the error corrections from EA1. EA4 combines all of the EAG's amendments together in a single analysis.

EA1: Correction of errors

The following corrections were applied to the company's updated model:

- *EA1a*: General population mortality risks were amended to use life tables for England for the period 2021-2023⁸⁷ (rather than England and Wales).
- *EA1b*: The costs of BSC pain medications were amended to reflect the lowest cost products listed on the BNF²⁶ or eMIT.⁸⁰ The revised costs used in the analyses are shown in Table 48.
- *EA1c*: The formulae used to draw probabilistic samples of the coefficients of the exponential model for TTD were amended to use the log mean of the rate parameter and the SE, with the sampled log rate then exponentiated back onto the natural scale (see footnotes to Table 46).

These model corrections are included in all subsequent exploratory analyses.

Table 48: BSC drug acquisition costs applied in EAG's preferred analyses

Drug, dose	Units per pack	Drug cost applied in company's updated model	Drug cost applied in EAG's preferred analyses	EAG cost source
Co-codamol, 30/500mg QDS	100	£2.74	£1.93	eMIT ⁸⁰
Tramadol capsules, 100mg QDS	100	£2.20	£0.84	BNF ²⁶
Paracetamol tablets, 1g QDS	100	£0.79	£0.79	eMIT ⁸⁰
Morphine sulfate, 30mg IR every 4 hours	56	£5.31	£4.75	BNF ²⁶
	56	£10.61	£9.50	BNF ²⁶
Dexamethasone, 4mg OD	50	£35.97	£35.97	eMIT ⁸⁰

EAG - External Assessment Group; QDS - four times daily; IR - immediate release; OD - once daily; eMIT - Electronic Market Information Tool; BNF - British National Formulary

EA2: Selection of alternative BID-unadjusted OS function for ripretinib group and alternative switching-adjusted OS function for BSC group

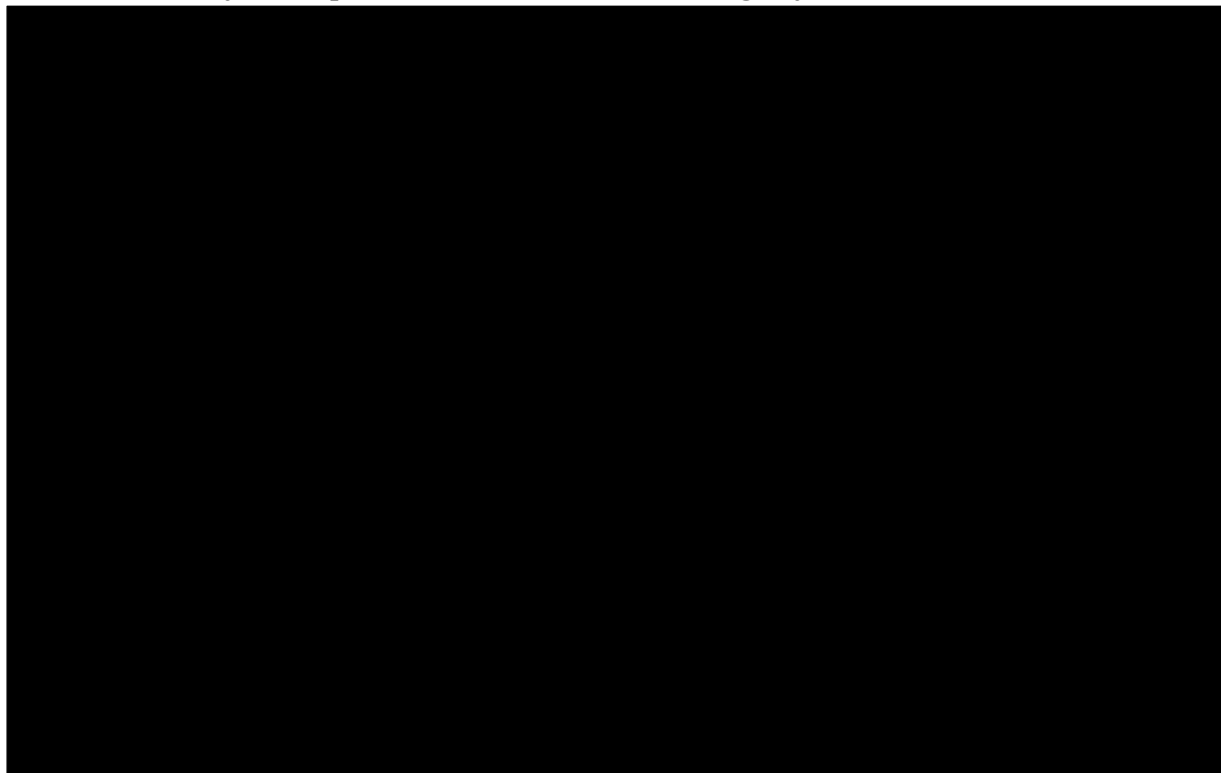
Within this analysis, the model was amended to apply the exponential distribution to the BID-unadjusted OS data in the ripretinib group and the generalised gamma distribution to the switching-adjusted OS data for in BSC group. These alternative model selections were based on advice received from the EAG's clinical advisors (see Table 45).

EA3: Adjustment of BID dose adjustment in the ripretinib OS data

Within this analysis, ripretinib OS was amended to use the BID-adjusted survival models based on the two-stage estimation method. The analysis applies the complex two-stage estimation method using the generalised gamma model, including re-censoring. The log-logistic model fitted to the BID-adjusted OS data was then selected for inclusion in the analysis because: (a) the hazard function provides a good representation of the underlying data (see Figure 35) and (b) this model gives a 10-year OS prediction of █████ which is close to the consensus estimate of █████ provided by the clinical experts who attended the company's 2024 advisory board meeting⁴⁰ (see Figure 36). This estimate is also similar to the 10-

year OS estimate for the unadjusted Weibull and exponential models applied in EA2. This analysis retains the company's preferred log-logistic model for OS in the BSC group.

Figure 36: Observed and model-predicted OS using the company's preferred BID-unadjusted ripretinib model, the EAG's preferred BID-unadjusted and BID-adjusted ripretinib models and the switching-adjusted BSC data



EAG - External Assessment Group; OS - overall survival; BSC - best supportive care

EA4: EAG's preferred analysis

This analysis combines EAG analyses 1-3. The EAG's preferred analysis was conducted using both the deterministic and probabilistic versions of the model. This analysis uses the BID-adjusted OS data in the ripretinib group and is intended to reflect the situation whereby ripretinib is given only at a dose of 150mg QD. For OS in the BSC group, this analysis uses the generalised gamma model fitted to the switching-adjusted OS data. If BID dosing is permitted, the models presented in ASA1 will be more relevant for informing decision-making.

5.2.3 EAG's additional sensitivity analyses

The EAG undertook the following additional sensitivity analyses using the deterministic version of the EAG's preferred model (EA4a):

- *ASA1a-f*: These analyses apply alternative parametric survival models fitted to the BID-unadjusted OS data and include the costs of BID dosing for 60.1% of the post-progression treatment duration (this percentage is based on the experience of INVICTUS,² see clarification response,³⁵ question B16). These analyses are intended to reflect the situation whereby post-progression ripretinib 150mg BID dosing is permitted.

- *ASA2a-f*: These analyses apply alternative parametric survival models fitted to the BID-adjusted ripretinib OS data using the complex 2-stage method (generalised gamma) with re-censoring and exclude the costs of BID dosing. These analyses are based on the same BID adjustment analysis as the EAG's preferred model and explore the impact of selecting alternative parametric survival models fitted to the BID-adjusted OS data.
- *ASA3a-f*: These analyses apply alternative parametric survival models fitted to the BID-adjusted ripretinib OS data using the complex 2-stage method (generalised gamma) without re-censoring and exclude the costs of BID dosing. These analyses are equivalent to ASA2 but remove the impact of re-censoring.
- *ASA4a-f*: These analyses were conducted to explore the impact of selecting alternative parametric survival models for TTD for ripretinib.
- *ASA5a-f*: These analyses were conducted to explore the impact of selecting alternative parametric survival models for PFS for both ripretinib and BSC.
- *ASA6a-f*: These analyses were conducted to explore the impact of alternative methods for adjusting BSC OS to account for treatment switching in the placebo group of INVICTUS.²
- *ASA7*: This analysis was conducted to explore the impact of applying an alternative health state utility value to the PD state based on the GRID study⁸⁸ (utility value PD off treatment for ripretinib and PD for BSC = 0.647 rather than 0.624).
- *ASA8*: These analyses explore the impact of all BID-adjustment models used to adjust OS and all parametric survival models fitted to the BID-adjusted OS data. Results for each analysis are presented graphically using separate plots which highlight the impact of including re-censoring.

5.2.4 EAG exploratory analysis - results

5.2.4.1 Results of the EAG's preferred analysis

The results of the EAG's preferred analysis of ripretinib versus BSC are presented in Table 49. All ICERs including QALY weighting reflect a decision modifier of 1.7. Unless otherwise stated, all analyses are intended to reflect a situation whereby ripretinib is used at a dose of 150mg QD (i.e., where BID dosing is not used). Correcting the remaining errors in the company's updated model leads to an estimated ICER for ripretinib versus BSC of £28,703 per QALY gained (EA1); this is slightly lower than the company's base case ICER. The inclusion of the exponential model fitted to the BID-unadjusted ripretinib OS data and the generalised gamma model fitted to the switching-adjusted BSC OS data increases the ICER to £36,321 per QALY gained (EA2). The inclusion of the log-logistic model fitted to the BID-adjusted ripretinib OS data, whilst retaining the company's preferred log-logistic model for BSC OS, leads to an ICER of £55,113 per QALY gained (EA3). The EAG's preferred analysis (EA4b) which includes all of the EAG's preferred assumptions (including BID-adjusted ripretinib OS) results in a probabilistic ICER of £55,470 per QALY gained. The ICER based on the deterministic version of the model is lower at £52,822 per QALY gained (EA4a).

Table 49: EAG preferred analysis results – ripretinib versus BSC, decision modifier = 1.7

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER (excl. DM)	ICER (incl. DM)
Company's updated base case model, deterministic								
Ripretinib	3.72			3.34			£48,842	£28,730
BSC	0.38			-	-	-	-	-
EA1: Correction of errors								
Ripretinib	3.72			3.34			£48,796	£28,703
BSC	0.38			-	-	-	-	-
EA2: Selection of alternative OS models fitted to BID-unadjusted OS data (ripretinib = exponential; BSC = generalised gamma)								
Ripretinib	2.52			2.21			£61,745	£36,321
BSC	0.31			-	-	-	-	-
EA3: Inclusion of BID-adjusted OS for ripretinib group; generalised gamma, 2-stage, complex model with re-censoring (ripretinib = log-logistic; BSC = log-logistic)								
Ripretinib	1.79			1.40			£93,693	£55,113
BSC	0.38			-	-	-	-	-
EA4a: EAG-preferred analysis, deterministic[†]								
Ripretinib	1.79			1.47			£89,797	£52,822
BSC	0.31			-	-	-	-	-
EA4b: EAG-preferred analysis, probabilistic[†]								
Ripretinib	N/R			NR			£94,299	£55,470
BSC	N/R			-	-	-	-	-

EAG - External Assessment Group; LYG - life year gained; QALY - quality-adjusted life year; DM - decision modifier; TTD - time to treatment discontinuation; OS - overall survival; BSC - best supportive care; BID - twice daily; NR - not reported

* Undiscounted

[†]This analysis uses the log-logistic model fitted to the BID-adjusted ripretinib OS data

5.2.4.2 Results of the EAG's additional sensitivity analysis

The results of ASA1-7 are shown in Table 50. The results indicate the following:

- The selection of alternative parametric survival models fitted to the BID-unadjusted ripretinib OS data together with the inclusion of the costs of BID dosing for 60.1% of post-progression time leads to ICERs ranging from £31,457 to £43,807 per QALY gained (ASA1). These analyses reflect a situation whereby post-progression BID dosing is permitted. Whilst there is uncertainty around the effect of ripretinib 150mg BID dosing on long-term OS, it is noteworthy that all of these analyses result in ICERs which are lower than the EAG's preferred (BID-adjusted) analysis. As expected, the ICER for ripretinib versus BSC is higher when either the exponential or Weibull models are selected as these distributions produce less favourable OS projections compared with the other survival models (see Figure 26).
- The selection of alternative parametric survival models fitted to the BID-adjusted ripretinib OS data (with re-censoring) leads to ICERs ranging from £48,656 (log-normal) to £73,815 (Gompertz) per QALY gained (ASA2). The EAG's preferred analysis applies the log-logistic model for ripretinib and is towards the lower end of this ICER range.

- The selection of alternative parametric survival models fitted to the BID-adjusted ripretinib OS data (without re-censoring) leads to ICERs ranging from £21,813 to £45,589 per QALY gained (ASA3). These ICERs are markedly lower than the equivalent analyses in ASA2 which include re-censoring.
- The selection of alternative parametric models for TTD leads to ICERs ranging from £52,469 (Weibull) to £61,355 (log-logistic) per QALY gained (ASA4). The EAG's preferred analysis using the exponential model is towards the lower end of this range.
- The model is not particularly sensitive to the selected parametric survival model for PFS, with all ICERs ranging from £52,473 (Weibull) to £55,031 (log-logistic) per QALY gained (ASA5).
- The ICER is sensitive to the method used to adjust for treatment switching in the BSC group (ASA6). The ICER is substantially higher when the OS data are not adjusted (£154,896 per QALY gained).
- The use of an alternative utility value for the PD (off treatment/BSC) state based on GRID has a minimal effect on the ICER (ASA7).

Table 50: EAG additional sensitivity analysis results – ripretinib versus BSC

Scenario	Inc. QALYs	Inc. Costs	ICER excl. DM	ICER incl. DM	DM
Base case / preferred analysis					
Company's updated base case, deterministic			£48,842	£28,730	1.7
EAG's preferred analysis, deterministic (EA4)			£89,797	£52,822	1.7
ASA1: Alternative OS models unadjusted for BID dosing, includes BID dosing costs for 60.1% of post-progression time					
ASA1a – Exponential			£72,103	£42,414	1.7
ASA1b – Weibull			£74,472	£43,807	1.7
ASA1c – Gompertz			£53,476	£31,457	1.7
ASA1d – Log-normal			£54,176	£31,868	1.7
ASA1e – Log-logistic			£55,637	£32,727	1.7
ASA1f – Generalised gamma			£56,603	£33,296	1.7
ASA2: Alternative OS models adjusted for BID (generalised gamma, complex 2-stage with re-censoring), includes QD dosing costs only					
ASA2a – Exponential			£96,172	£56,572	1.7
ASA2b – Weibull			£123,487	£72,639	1.7
ASA2c – Gompertz			£125,485	£73,815	1.7
ASA2d – Log-normal			£82,715	£48,656	1.7
ASA2e – Log-logistic			£89,797	£52,822	1.7
ASA2f – Generalised gamma			£123,875	£72,868	1.7
ASA3: Alternative OS models adjusted for BID (generalised gamma, complex 2-stage without re-censoring), includes QD dosing costs only					
ASA3a – Exponential			£76,686	£45,110	1.7
ASA3b – Weibull			£77,502	£45,589	1.7
ASA3c – Gompertz			£37,082	£21,813	1.7
ASA3d – Log-normal			£58,305	£34,297	1.7
ASA3e – Log-logistic			£59,042	£34,731	1.7
ASA3f – Generalised gamma			£51,254	£30,149	1.7
ASA4: Alternative TTD models					
ASA4a – Exponential			£89,797	£52,822	1.7
ASA4b – Weibull			£89,197	£52,469	1.7
ASA4c – Gompertz			£90,131	£53,018	1.7
ASA4d – Log-normal			£100,059	£58,858	1.7
ASA4e – Log-logistic			£104,303	£61,355	1.7

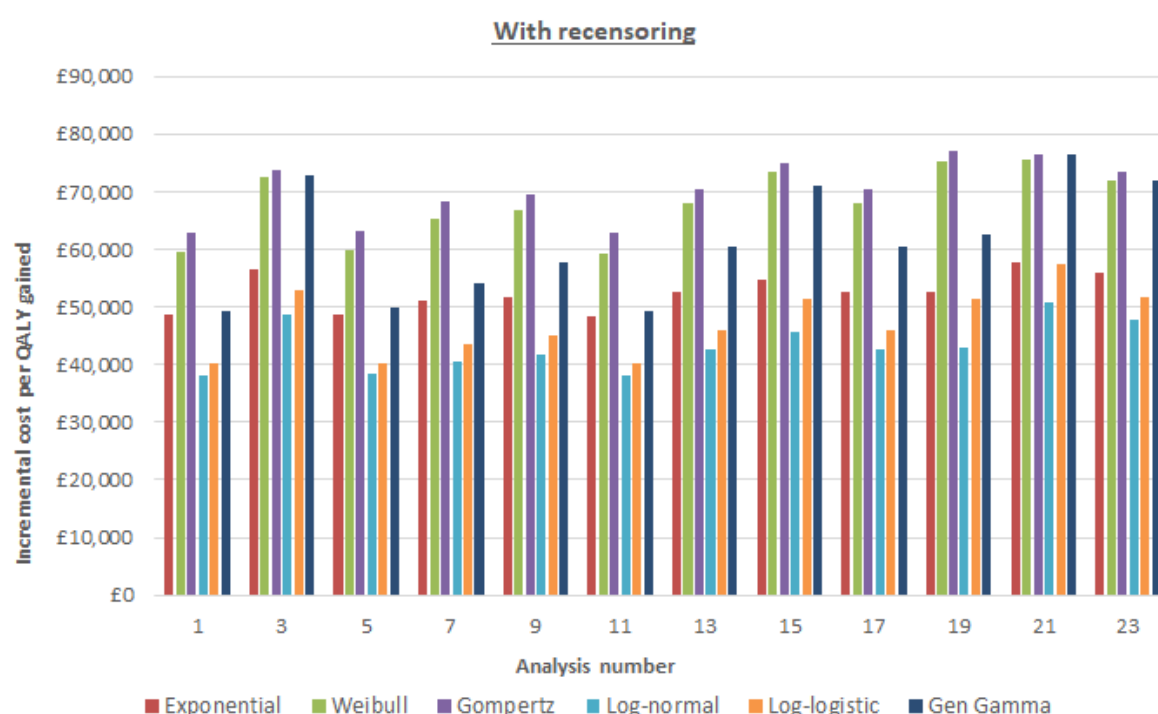
Scenario	Inc. QALYs	Inc. Costs	ICER excl. DM	ICER incl. DM	DM
ASA4f – Generalised gamma			£91,166	£53,627	1.7
ASA5: Alternative PFS models					
ASA5a – Exponential			£89,238	£52,493	1.7
ASA5b – Weibull			£89,204	£52,473	1.7
ASA5c – Gompertz			£89,351	£52,559	1.7
ASA5d – Log-normal			£89,797	£52,822	1.7
ASA5e – Log-logistic			£93,553	£55,031	1.7
ASA5f – Generalised gamma			£89,286	£52,521	1.7
ASA6: Alternative placebo group switching adjustment					
ASA6a – OS: Unadjusted*			£263,323	£219,436	1.2
ASA6b – OS: Two-stage adjusted simple without re-censoring			£91,704	£53,944	1.7
ASA6c – OS: Two-stage adjusted complex without re-censoring			£97,741	£57,494	1.7
ASA6d – OS: Two-stage adjusted complex with re-censoring			£94,468	£55,569	1.7
ASA6e – OS: RPSFTM-adjusted without re-censoring			£94,437	£55,551	1.7
ASA6f – OS: RPSFTM-adjusted with re-censoring			£82,916	£48,774	1.7
ASA6g – OS: RPSFTM-adjusted with common treatment effect relaxed (k _i =0.5; Weibull)			£84,596	£49,763	1.7
ASA6h – OS: RPSFTM-adjusted with common treatment effect relaxed (k _i =0.5)			£111,251	£65,442	1.7
ASA7: Alternative health state utility values					
ASA7 – GRID utility values			£88,981	£52,342	1.7

EAG - External Assessment Group; BSC - best supportive care; Inc. - incremental; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; DM - decision modifier; EA - exploratory analysis; ASA - additional sensitivity analysis; OS - overall survival; BID - twice daily; QD - once daily; TTD - time to treatment discontinuation; PFS - progression-free survival; RPSFTM - rank-preserving structural failure time model

The results of ASA8 are shown in Figure 37 (Panel A = ICERs for all adjustment models including re-censoring; Panel B = ICERs for all adjustment models excluding re-censoring). The analyses indicate that the ICER is sensitive both to the specification of the BID adjustment model for OS as well as the choice of parametric survival model fitted to the BID-adjusted OS data. The figure indicates that adjusting OS for BID dosing including re-censoring leads to comparatively higher ICERs compared with the equivalent adjustment models without re-censoring (ICER range for adjustment models including re-censoring = £38,093 to £77,043; ICER range for adjustment models excluding re-censoring = £20,416 to £47,646).

Figure 37: Additional sensitivity analysis 8 – exploratory analysis of all simple and complex BID adjustment models for OS

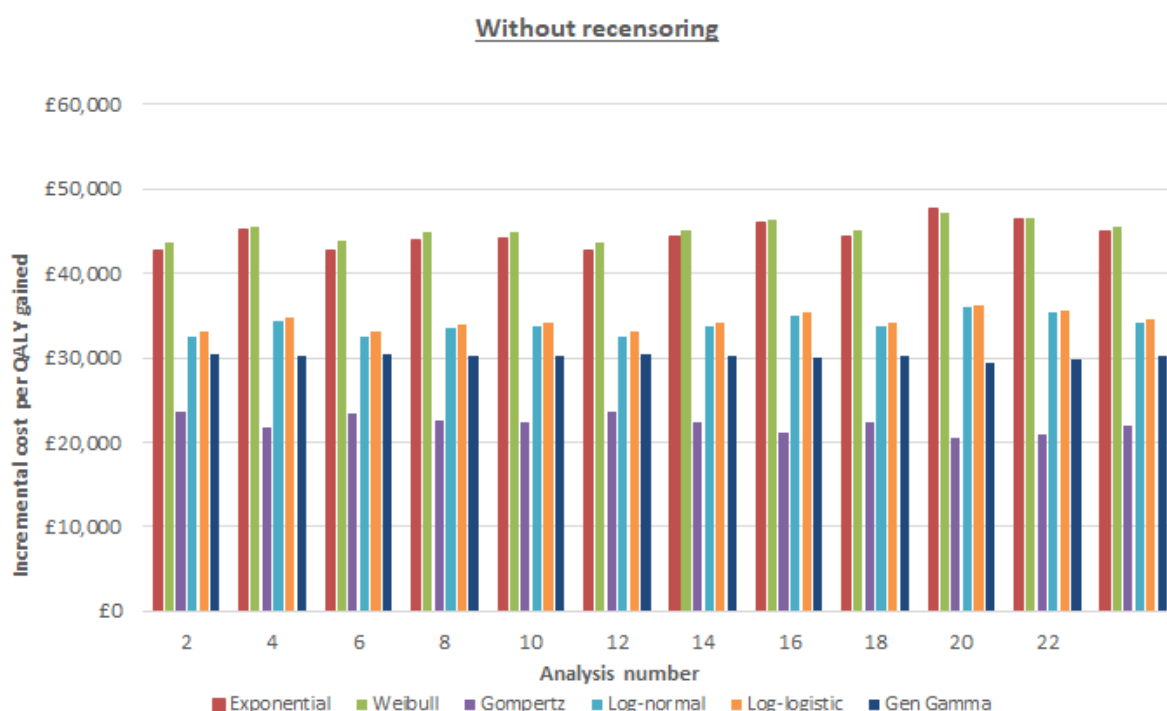
A: Models including re-censoring



Analysis key

- Analysis no. 1: OS – QD to BID Crossover (Two stage model: Complex, Exponential)
- Analysis no. 3: OS – QD to BID Crossover (Two stage model: Complex, Generalised Gamma)
- Analysis no. 5: OS – QD to BID Crossover (Two stage model: Complex, Gompertz)
- Analysis no. 7: OS – QD to BID Crossover (Two stage model: Complex, Log-Logistic)
- Analysis no. 9: OS – QD to BID Crossover (Two stage model: Complex, Log-Normal)
- Analysis no. 11: OS – QD to BID Crossover (Two stage model: Complex, Weibull)
- Analysis no. 13: OS – QD to BID Crossover (Two stage model: Simple, Exponential)
- Analysis no. 15: OS – QD to BID Crossover (Two stage model: Simple, Generalised Gamma)
- Analysis no. 17: OS – QD to BID Crossover (Two stage model: Simple, Gompertz)
- Analysis no. 19: OS – QD to BID Crossover (Two stage model: Simple, Log-Logistic)
- Analysis no. 21: OS – QD to BID Crossover (Two stage model: Simple, Log Normal)
- Analysis no. 23: OS – QD to BID Crossover (Two stage model: Simple, Weibull).

B: Models excluding re-censoring



Analysis key

- Analysis no. 2: OS – QD to BID Crossover (Two stage model: Complex, Exponential)
- Analysis no. 4: OS – QD to BID Crossover (Two stage model: Complex, Generalised Gamma)
- Analysis no. 6: OS – QD to BID Crossover (Two stage model: Complex, Gompertz)
- Analysis no. 8: OS – QD to BID Crossover (Two stage model: Complex, Log-Logistic)
- Analysis no. 10: OS – QD to BID Crossover (Two stage model: Complex, Log-Normal)
- Analysis no. 12: OS – QD to BID Crossover (Two stage model: Complex, Weibull)
- Analysis no. 14: OS – QD to BID Crossover (Two stage model: Simple, Exponential)
- Analysis no. 16: OS – QD to BID Crossover (Two stage model: Simple, Generalised Gamma)
- Analysis no. 18: OS – QD to BID Crossover (Two stage model: Simple, Gompertz)
- Analysis no. 20: OS – QD to BID Crossover (Two stage model: Simple, Log-Logistic)
- Analysis no. 22: OS – QD to BID Crossover (Two stage model: Simple, Log Normal)
- Analysis no. 24: OS – QD to BID Crossover (Two stage model: Simple, Weibull).

5.3 Decision modifiers

5.3.1 QALY weighting for severity

Based on the characteristics of patients in INVICTUS (mean age = 60.1 years; 43.41% female) and the company's mean estimate of the QALYs for the BSC comparator group (■■■■ QALYs), the York Shortfall Calculator⁷⁶ suggests an absolute shortfall of ■■■■ QALYs and a proportional shortfall of ■■■■. This indicates that a decision modifier of 1.7 is appropriate. The EAG's preferred analysis applies a generalised gamma distribution for OS in the BSC group resulting in less health gain in the comparator group (■■■■ QALYs), thereby also indicating that a decision modifier of 1.7 is appropriate.

5.3.2 Uncaptured benefits

The CS³ does not make a case that there are any relevant benefits of ripretinib which have not been captured in the ICER.

5.3.4 Health inequalities

The CS³ states that there are no special considerations relating to health inequity or inequality.

5.4 Confidential comparator and subsequent treatment prices

All analyses presented in this report include the proposed PAS for ripretinib. None of the other drugs included in the base case model are subject to comparator PAS discounts or confidential NHS prices.

5.5 Discussion

The CS³ includes an SLR of existing economic studies of treatments for GIST and details the methods and results of a *de novo* model-based health economic analysis of ripretinib versus BSC in patients who have had at least three prior therapies for advanced or metastatic GIST, including imatinib.

The company's SLR identified one existing economic model of 4L+ ripretinib versus BSC (Liao *et al.*⁵⁹). This published economic analysis is limited due the absence of any statistical adjustment to account for confounding of the OS data caused by treatment switching in the placebo group of INVICTUS and because it excludes post-progression ripretinib costs from the intervention group of the model.

The company's economic model assesses the cost-effectiveness of ripretinib (plus BSC) versus BSC alone for the 4L+ treatment of patients with advanced GIST. The model uses a partitioned survival approach which includes four health states: (i) progression-free; (ii) progressed disease (on treatment); (iii) progressed disease (off treatment/BSC), and (iv) dead. The analysis adopts an NHS and PSS perspective, including QALYs accrued by GIST patients; caregiver effects are not included. Clinical outcomes for both treatment groups are based on parametric survival models fitted to data on PFS and OS from INVICTUS,² including the adjustment of OS in the BSC group to account for treatment switching using the two-stage estimation method (with re-censoring). Patients in the intervention group are assumed to receive treatment with ripretinib prior to and following disease progression. Whilst patients in INVICTUS were allowed to dose-escalate to ripretinib 150mg BID after progression, the company's base case model does not include any statistical adjustment to account for the effect of BID dosing on OS, whilst the drug acquisition costs assume ripretinib 150mg QD dosing for all patients. Health state utility values are based on an MMRM fitted to EQ-5D-5L data (mapped to the 3L version) from INVICTUS; resource use and cost parameters were taken from a clinical expert survey used in TA488,⁴⁵ standard costing sources^{26, 67} and other literature.⁶⁸

The probabilistic version of the company's updated model suggests that the ICER for ripretinib versus BSC is expected to be £28,576 per QALY gained. The deterministic ICER is similar at £28,730 per QALY gained.

The EAG critically appraised the company's health economic analysis and double-programmed the deterministic version of the company's model. The EAG notes the following key concerns regarding the company's economic model:

- The company's model is informed by data from the January 2021 DCO of INVICTUS.² A later DCO of May 2022 is available for OS and safety data. However, this later data-cut has not been used in the company's model. The EAG considers that the reliance on the 2021 DCO unnecessarily increases uncertainty around the modelled estimates of OS for ripretinib.
- The company's base case analysis uses the log-logistic distribution for ripretinib OS, based on the BID-unadjusted OS data. This model suggests a predicted probability of OS at 10 years of [REDACTED]. The clinical experts who attended the company's 2024 advisory board meeting stated that a predicted probability of OS at 10 years for ripretinib of [REDACTED] was an overestimate and that [REDACTED] was more realistic. One clinician considered that an estimate of [REDACTED] was plausible because treatments are improving and new options are being developed; however, the EAG notes that this expert's estimate does not reflect expected OS if ripretinib was included in the current treatment pathway for GIST.⁴⁰ The EAG's clinical advisors preferred the selection of the exponential and Weibull models fitted to the BID-unadjusted ripretinib OS data. These models are less optimistic than the company's selected log-logistic distribution as they suggest predicted probabilities of OS at 10 years of approximately [REDACTED].
- Clinical experts consulted by the company and the EAG have indicated that ripretinib 150mg BID dosing is expected to lead to improved OS compared with 150mg QD dosing. However, BID dosing represents an off-label use of ripretinib. The EAG's clinical advisors stated that they would want to use BID dosing where clinically appropriate if the commissioning route for ripretinib allowed this. There remains uncertainty around whether NHS England will commission BID dosing. The company's base case analysis uses the BID-unadjusted OS data from INVICTUS² (which includes the effects of BID dosing in some patients) and includes the costs of ripretinib 150mg QD dosing only. Taken together, the company's model assumes that the outcomes observed in INVICTUS (including the effects of post-progression ripretinib 150mg BID dosing in some patients) can be achieved by using the 150mg QD dose in all patients. The EAG believes that these assumptions result in an inconsistency between the outcomes observed in the trial and the resources required to generate those outcomes. As part of its clarification response,³⁵ the company conducted additional analyses to adjust the OS data to account for BID dosing using the two-stage estimation method and refitted survival models to the BID-adjusted ripretinib OS data. These analyses form part of the EAG's preferred analyses, based on the assumption that only QD dosing would be commissioned. The EAG's sensitivity analyses include the use of parametric survival models fitted to the BID-unadjusted OS data and the inclusion of the costs of BID dosing in 60.1% of the post-progression ripretinib

treatment time, based on INVICTUS. The latter analyses may be more relevant for decision-making if BID dosing is commissioned.

The EAG undertook exploratory analyses using the company's updated model to address the issues described above. The EAG's preferred model includes: (i) the correction of errors; (ii) the selection of an alternative model for OS in the BSC group (OS data adjusted for switching using the simple two-stage estimation method [log-normal] with re-censoring; generalised gamma model fitted to the switching-adjusted data) and (iii) the selection of an alternative model for OS in the ripretinib group (OS data adjusted for ripretinib 150mg BID dosing using the complex two-stage estimation method [generalised gamma] with re-censoring; log-logistic model fitted to the BID-adjusted data). The probabilistic version of the EAG's preferred model suggests that the ICER for ripretinib versus BSC is expected to be £55,470 per QALY gained. The deterministic version of the model suggests an ICER of £52,822 per QALY gained. These estimates are substantially higher than the company's base case ICER.

The EAG's preferred analyses assume that BID dosing would not be commissioned in the NHS. However, this assumption may not be appropriate. The EAG's additional sensitivity analyses indicate that fitting survival models to the BID-unadjusted OS data for ripretinib and including the costs of BID dosing for 60.1% of the ripretinib post-progression treatment time leads to lower ICERs which range from £31,457 to £43,807 per QALY gained. These analyses may be more relevant for decision-making if BID dosing is permitted. The EAG's other sensitivity analyses indicate that the ICER is sensitive to the choice of parametric survival model for OS, whether the adjustment model for OS to account for the effects of BID dosing includes re-censoring, whether the BSC OS data are adjusted for treatment switching, and the choice of parametric survival model selected for TTD.

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**Division of
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**Ripretinib for treating advanced gastrointestinal stromal tumours after 3
or more treatments (review of TA881) [ID6496]**

**External Assessment Group addendum – comments on the company’s
updated base case analysis**

Produced by	Sheffield Centre for Health and Related Research (SCHARR), The University of Sheffield
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Date completed	25 th September 2025

1. Introduction

In September 2025, the company submitted an addendum which contains the results of its updated base case analysis¹ together with an updated version of the executable model. The company's updated base case analysis is based on the deterministic version of EAG's preferred model (see EAG report,² Table 49, Scenario EA4a), but features two differences:

- (1) The EAG's preferred analysis (EA4) applied a two-stage adjustment to account for intra-patient dose escalation (IPDE) in the ripretinib arm of the INVICTUS trial³ using a complex generalised gamma model *with re-censoring* and the *log-logistic* model for extrapolation. In contrast, the company has retained the two-stage adjustment using the complex generalised gamma model but has selected the *without re-censoring* scenario and adopted the *log-normal* model for extrapolation of the adjusted data.
- (2) The company has increased the Patient Access Scheme (PAS) discount for ripretinib from [REDACTED] to [REDACTED].

The company's addendum document is limited to a table which contains the results of model analyses. It does not contain any explanatory text regarding why the company prefers to exclude re-censoring from the ripretinib IPDE adjustment model or why the parametric survival model used for extrapolation of the adjusted data has been changed. The EAG also notes that the version of the model submitted by the company does not include the correction of errors implemented by the EAG (see EAG report,² Section 5.2.2, EA1).

2. EAG comments on the company's updated analysis

As discussed in the EAG report,² re-censoring is applied to guard against informative censoring in the counterfactual dataset, although this comes at the cost of losing longer-term survival information which is needed for extrapolation.⁴ Decision Support Unit (DSU) Technical Support Document (TSD) 24 recommends presenting results with and without re-censoring for two-stage adjustment analyses.⁵ As such, the EAG acknowledges that it is appropriate to present the two-stage-IPDE-adjusted results for ripretinib without re-censoring. However, the EAG believes that the scenario including re-censoring should be preferred for the reasons described below.

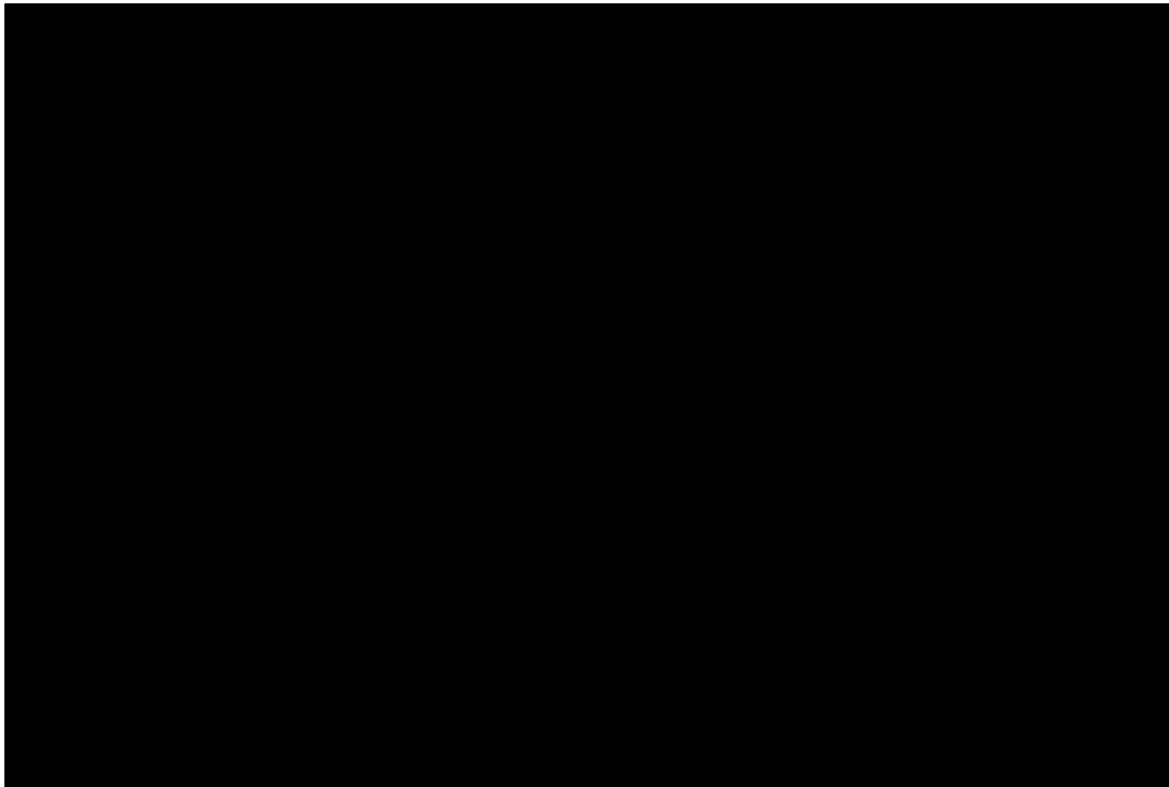
Firstly, the company's updated base case model (including two-stage adjustment with the complex generalised gamma without re-censoring; log-normal extrapolation) results in a 10-year probability of overall survival (OS) for ripretinib-treated patients of [REDACTED] (see Figure 1); this is more optimistic than the consensus estimate of [REDACTED] provided by clinical experts at the company's 2024 advisory board meeting.⁶ The EAG's preferred analysis (including two-stage adjustment with the complex generalised gamma with re-censoring; log-logistic extrapolation) results in a predicted 10-year OS probability of [REDACTED] which is similar to, albeit slightly lower than, the consensus estimate obtained from the clinicians

consulted by the company. The EAG also notes that based on the unadjusted ripretinib OS data, the EAG's clinical advisors' preferred OS models for extrapolation (Weibull and exponential) suggested 10-year OS probabilities of [REDACTED] and [REDACTED], respectively.

Secondly, the EAG notes that the smoothed empirical hazard of the counterfactual Kaplan-Meier function for OS in the without re-censoring scenario (see Figure 2, provided as part of the company's clarification response⁷) suggests an initial increase up to around 40 weeks, followed by another rise at approximately 93 weeks. The late upward turning point may be an artefact of data sparsity at later follow-up time points, right-censoring, and/or bandwidth choice for smoothing, and is not necessarily a true rise in risk. Nonetheless, a true late hazard increase may be clinically possible (e.g., due to treatment effect waning). Without more mature OS data, the EAG cannot conclude either way. More mature follow-up would provide greater confidence in the extrapolation. The EAG also notes that none of the survival extrapolation models that capture the initial hazard increase (the log-logistic, log-normal, and the generalised gamma distributions) provide a satisfactory fit to the without re-censoring two-stage adjusted data (i.e., the timing of the first peak of hazard increase). Among the standard extrapolation models assessed in this scenario, the log-logistic model appears to provide a better fit than the log-normal model, as its hazard peak aligns more closely with the empirical hazard (Figure 2), and survival is closer to the counterfactual Kaplan-Meier curve for the majority of the follow-up period (Figure 3), though overall fit remains sub-optimal. The predicted 10-year OS under the log-logistic model in the without re-censoring scenario ([REDACTED]) still exceeds the aforementioned expert consensus estimate ([REDACTED]). As previously shown in Figure 34 and Figure 35 of the EAG report,² the with re-censoring scenario—using the complex generalised gamma model for IPDE adjustment and the log-logistic model for extrapolation—generates a predicted probability of 10-year OS of [REDACTED], which was consistent with estimates provided by the EAG's clinical advisors and most of the clinical advisors consulted by the company.

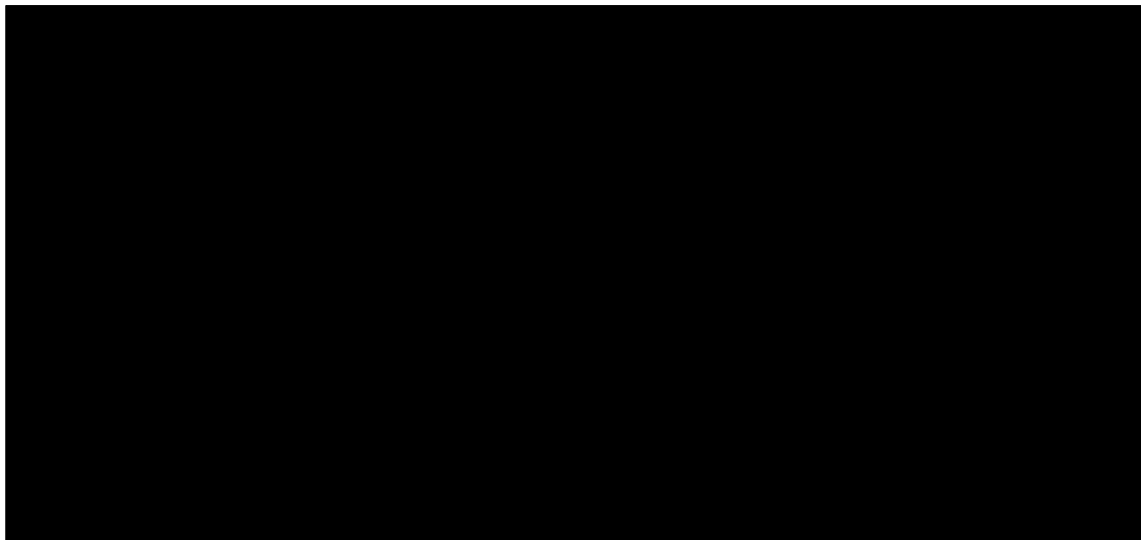
The EAG considers that the point estimate of the incremental cost-effectiveness ratio (ICER) may fall between £44,964 per quality-adjusted life year (QALY) gained (the EAG's preferred scenario: two-stage adjustment of the IPDE using a complex generalised gamma model with re-censoring and log-logistic extrapolation) and £29,717 per QALY gained (the equivalent scenario but excluding re-censoring). However, the EAG regards its preferred model specification as being the most appropriate, given the sub-optimal fit of the extrapolation models in the without re-censoring scenario and the more optimistic 10-year OS predictions compared with clinical expert opinion obtained by the company and the EAG.

Figure 1: Model predictions of OS in company's previous and new base cases and EAG preferred analysis, ripretinib and BSC (generated by the EAG using the company's model)



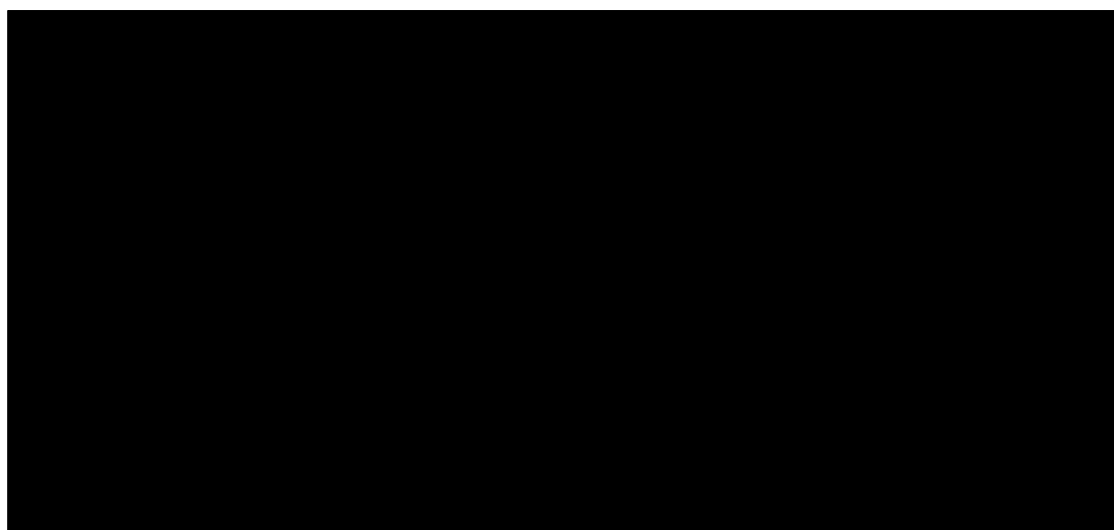
OS - overall survival; EAG - External Assessment Group; BSC - best supportive care

Figure 2: Empirical and modelled hazard functions based on the complex 2-stage estimation BID-adjustment (generalised gamma) without re-censoring (reproduced from company's additional clarification response, 15th July 2025)



BID - twice daily; QD - once daily

Figure 3: Kaplan-Meier estimates and model predictions of OS based on the complex 2-stage estimation BID-adjustment (generalised gamma) without re-censoring (reproduced from company's additional clarification response, 15th July 2025)



BID - twice daily; QD - once daily

3. Updated model results

The results of the company's updated base case analysis and the EAG's exploratory analysis, including the EAG's preferred analysis (EA4a), are shown in Table 1. All of these analyses include a decision modifier of 1.7. The deterministic version of the company's updated base case model suggests that the ICER for ripretinib versus best supportive care (BSC) is £29,350 per QALY gained. This is markedly lower than the EAG's preferred ICER of £44,964 per QALY gained. The probabilistic versions of the company's updated base case model and the EAG's preferred model result in higher ICERs of £30,232 and £47,162 per QALY gained, respectively (see Table 2).

The EAG also conducted an additional analysis, starting from the company's updated base case scenario, whereby the parametric survival model used for extrapolation of the adjusted ripretinib OS data was changed to the log-logistic distribution. This had only a minor impact on the ICER (company's base case ICER = £29,350; log-logistic model ICER = £29,717 per QALY gained).

The company's addendum also includes the results of several other scenario analyses. However, these are based on the EAG's preferred analysis (EA4a) including the updated ripretinib PAS rather than the company's updated base case analysis. For completeness, these scenarios have been reproduced in Table 3.

Table 1: EAG preferred analysis results – ripretinib versus BSC, decision modifier = 1.7, deterministic

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER (excl. DM)	ICER (incl. DM)
Company's base case model (at clarification), deterministic (previous PAS)								
Ripretinib	3.72			3.34			£48,842	£28,730
BSC	0.38			-	-	-	-	-
Company's base case model (at clarification), deterministic (new PAS)								
Ripretinib	3.72			3.34			£41,928	£24,663
BSC	0.38			-	-	-	-	-
EA1: Correction of errors (new PAS)								
Ripretinib	3.72			3.34			£41,882	£24,637
BSC	0.38			-	-	-	-	-
EA2: Selection of alternative OS models fitted to BID-unadjusted OS data (ripretinib = exponential; BSC = generalised gamma) (new PAS)								
Ripretinib	2.52			2.21			£52,789	£31,052
BSC	0.31			-	-	-	-	-
EA3: Inclusion of BID-adjusted OS for ripretinib group; generalised gamma, 2-stage, complex model with re-censoring (ripretinib = log-logistic; BSC = log-logistic) (new PAS)								
Ripretinib	1.79			1.40			£79,723	£46,896
BSC	0.38			-	-	-	-	-
EA4a: EAG-preferred analysis (BID-adjusted OS for ripretinib group; generalised gamma, 2-stage, complex model with re-censoring, log-logistic; BSC = generalised gamma) (new PAS)								
Ripretinib	1.79			1.47			£76,439	£44,964
BSC	0.31			-	-	-	-	-
Company's updated base-case (BID-adjusted OS for ripretinib group; generalised gamma, 2-stage, complex model without re-censoring, log-normal; BSC = generalised gamma) (new PAS)								
Ripretinib	2.90			2.59			£49,895	£29,350
BSC	0.31			-	-	-	-	-
EAG Additional analysis: company's updated base-case + log-logistic OS for ripretinib (new PAS)								
Ripretinib	2.93			2.62			£50,518	£29,717
BSC	0.31			-	-	-	-	-

EAG - External Assessment Group; LYG - life year gained; QALY - quality-adjusted life year; DM - decision modifier; TTD - time to treatment discontinuation; OS - overall survival; BSC - best supportive care; BID - twice daily; NR - not reported

* Undiscounted

† This analysis uses the log-logistic model fitted to the BID-adjusted ripretinib OS data

Table 2: EAG preferred analysis results – ripretinib versus BSC, decision modifier = 1.7, probabilistic (1,000 iterations)

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER (excl. DM)	ICER (incl. DM)
Company's base case model (at clarification), deterministic (previous PAS)								
Ripretinib	N/R			N/R			£48,690	£28,641
BSC	N/R			-	-	-	-	-
Company's base case model (at clarification), deterministic (new PAS)								
Ripretinib	N/R			N/R			£42,061	£24,742
BSC	N/R			-	-	-	-	-
EA4a: EAG-preferred analysis (BID-adjusted OS for ripretinib group; generalised gamma, 2-stage, complex model with re-censoring, log-logistic; BSC = generalised gamma) (new PAS)								
Ripretinib	N/R			N/R			£80,176	£47,162
BSC	N/R			-	-	-	-	-
Company's updated base-case (BID-adjusted OS for ripretinib group; generalised gamma, 2-stage, complex model without re-censoring, log-normal; BSC = generalised gamma) (new PAS)								
Ripretinib	N/R			N/R			£51,394	£30,232
BSC	N/R			-	-	-	-	-

EAG - External Assessment Group; LYG - life year gained; QALY - quality-adjusted life year; DM - decision modifier; TTD - time to treatment discontinuation; OS - overall survival; BSC - best supportive care; BID - twice daily; NR - not reported

* Undiscounted

† This analysis uses the log-logistic model fitted to the BID-adjusted ripretinib OS data

Table 3: EAG additional sensitivity analysis results – ripretinib versus BSC, decision modifier = 1.7, deterministic, new PAS

Scenario	Inc. QALYs	Inc. Costs	ICER excl. DM	ICER incl. DM
Base case / preferred analysis				
Company's updated base case, deterministic			£49,895	£29,350
EAG's preferred analysis, deterministic (EA4)			£76,439	£44,964
ASA1: Alternative OS models unadjusted for BID dosing, includes BID dosing costs for 60.1% of post-progression time				
ASA1a – Exponential			£61,534	£36,196
ASA1b – Weibull			£63,531	£37,371
ASA1c – Gompertz			£45,839	£26,964
ASA1d – Log-normal			£46,427	£27,310
ASA1e – Log-logistic			£47,659	£28,035
ASA1f – Generalised gamma			£48,471	£28,513
ASA2: Alternative OS models adjusted for BID (generalised gamma, complex 2-stage with re-censoring), includes QD dosing costs only				
ASA2a – Exponential			£81,809	£48,123
ASA2b – Weibull			£104,852	£61,678
ASA2c – Gompertz			£106,560	£62,682
ASA2d – Log-normal			£70,468	£41,452
ASA2e – Log-logistic			£76,439	£44,964
ASA2f – Generalised gamma			£105,183	£61,872
ASA3: Alternative OS models adjusted for BID (generalised gamma, complex 2-stage without re-censoring), includes QD dosing costs only				
ASA3a – Exponential			£65,383	£38,461
ASA3b – Weibull			£66,071	£38,865
ASA3c – Gompertz			£32,020	£18,835
ASA3d – Log-normal			£49,895	£29,350
ASA3e – Log-logistic			£50,518	£29,717
ASA3f – Generalised gamma			£43,955	£25,856
ASA4: Alternative TTD models				
ASA4a – Exponential			£76,439	£44,964
ASA4b – Weibull			£75,933	£44,666
ASA4c – Gompertz			£76,721	£45,130
ASA4d – Log-normal			£85,089	£50,053
ASA4e – Log-logistic			£88,667	£52,157
ASA4f – Generalised gamma			£77,592	£45,643

Scenario	Inc. QALYs	Inc. Costs	ICER excl. DM	ICER incl. DM
ASA5: Alternative PFS models				
ASA5a – Exponential			£75,978	£44,693
ASA5b – Weibull			£75,946	£44,674
ASA5c – Gompertz			£76,079	£44,752
ASA5d – Log-normal			£76,439	£44,964
ASA5e – Log-logistic			£79,594	£46,820
ASA5f – Generalised gamma			£76,015	£44,715
ASA6: Alternative placebo group switching adjustment				
ASA6a – OS: Unadjusted*			£222,722	£131,013
ASA6b – OS: Two-stage adjusted simple without re-censoring			£78,047	£45,910
ASA6c – OS: Two-stage adjusted complex without re-censoring			£83,136	£48,904
ASA6d – OS: Two-stage adjusted complex with re-censoring			£80,377	£47,281
ASA6e – OS: RPSFTM-adjusted without re-censoring			£80,351	£47,265
ASA6f – OS: RPSFTM-adjusted with re-censoring			£70,634	£41,549
ASA6g – OS: RPSFTM-adjusted with common treatment effect relaxed ($k_i=0.5$; Weibull)			£72,054	£42,385
ASA6h – OS: RPSFTM-adjusted with common treatment effect relaxed ($k_i=0.5$)			£94,523	£55,602
ASA7: Alternative health state utility values				
ASA7 – GRID utility values			£75,744	£44,555

EAG - External Assessment Group; BSC - best supportive care; Inc. - incremental; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; DM - decision modifier; EA - exploratory analysis; ASA - additional sensitivity analysis; OS - overall survival; BID - twice daily; QD - once daily; TTD - time to treatment discontinuation; PFS - progression-free survival; RPSFTM - rank-preserving structural failure time model

* Applies a decision modifier of 1.2

4. References

1. Deciphera Pharmaceuticals. Ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments (review of TA881) [ID6496]. Company's addendum including updated base case and updated PAS. Deciphera: London, UK; 2025.
2. Tappenden P, Essat M, Chang JYA, Navega Biz A, Ren k, Rawdin A, *et al.* Ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments (review of TA881) [ID6496]. External Assessment Group report. University of Sheffield: Sheffield, UK; 2025.
3. Deciphera Pharmaceuticals. A Phase 3, interventional, double-blind, placebo-controlled study to assess the safety and efficacy of DCC-2618 in patients with advanced gastrointestinal stromal tumors who have received treatment with prior anticancer therapies (INVICTUS). Clinical Study Report. Deciphera: Waltham, MA; 2019.
4. Latimer NR, White IR, Abrams KR, Siebert U. Causal inference for long-term survival in randomised trials with treatment switching: Should re-censoring be applied when estimating counterfactual survival times? *Statistical Methods in Medical Research* 2019;28(8):2475-93.
5. Bell Gorrod H, Latimer, N. R., Abrams K.R. . NICE DSU Technical Support Document 24: Adjusting survival time estimates in the presence of treatment switching: An update to TSD 16. 2024. NICE DSU: Sheffield, UK; 2024.
6. Deciphera Pharmaceuticals. DCPH-M00790 EXECUTIVE SUMMARY Advisory Board July 2024. Deciphera: Bristol, UK; 2024.
7. Deciphera Pharmaceuticals. Ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments (review of TA881) [ID6496]. Company's response to clarification questions from the EAG. Deciphera: Bristol, UK; 2025.

Single Technology Appraisal

Ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments (review of TA881) [ID6496]

EAG report – factual accuracy check and confidential information check

“Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.” (Section 5.4.9, [NICE health technology evaluations: the manual](#)).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Friday 15 August 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [REDACTED] should be highlighted in turquoise and all information submitted as [REDACTED] in pink.

Issue 1 Language regarding the positioning of ripretinib

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 12, table 1: "Mismatch between the company's intended target population and the patient population enrolled in the INVICTUS trial."	Potentially remove issue 1. Add SmpC reference.	Company positioning was communicated too narrowly in the CS (Section 1.4.2, page 24). Please consider the proposed for positioning for ripretinib to be in line with the NICE final scope, marketing authorisation and population included in the INVICTUS trial i.e. 4L+.	This is not a factual inaccuracy – the CS describes the proposed positioning of ripretinib as 4 th line therapy. However, the EAG has amended the report to state that the company clarified the intended target population at the factual accuracy check stage of the appraisal. All references to this issue have been removed from the EAG report.
Page 14: "However, there were some differences between INVICTUS and the company's proposed use of ripretinib. The company's positioning of ripretinib is at fourth-line (4L), whilst more than one-third of patients in INVICTUS had received more than three prior therapies (see Issue 1)."	~~"However, there were some differences between INVICTUS and the company's proposed use of ripretinib.~~ The company's positioning of ripretinib is at fourth-line or above (4L+), which is aligned with the patient population included in INVICTUS. " Add SmpC reference.	Company positioning was communicated too narrowly in the CS (Section 1.4.2, page 24). Please consider the proposed for positioning for ripretinib to be in line with the NICE final scope, marketing authorisation and population included in the INVICTUS trial i.e. 4L+.	Please refer to response to comment #1 in this block. The text has been amended as requested. A reference to the SmPC has not been included as this text is in the Executive Summary.
Page 14: "The CS states that the company intends to position	"The company intends to position ripretinib as 4L+ therapy (in patients	The 4L+ positioning aligns with the marketing authorisation, the	Please refer to response to comment #1 in this block.

ripretinib as 4L therapy (in patients who have received exactly three prior therapies – imatinib, sunitinib and regorafenib).”	who have received three or more prior therapies – including imatinib).” Add SmpC reference. Potentially remove ‘Issue 1’ table	final NICE scope and INVICTUS patient population. The label indication and final NICE scope only specifies ‘including imatinib.’	The box describing the issue based on the positioning of ripretinib described in the CS has been removed.
Page 23: “The company’s proposed positioning of ripretinib is as a fourth-line (4L) treatment for GIST (see Figure 1).”	“The company’s proposed positioning of ripretinib is as a fourth-line and above (4L+) treatment for GIST.” Add SmpC reference. Requires removal or update of Figure 1	Company positioning was communicated too narrowly in the CS (Section 1.4.2, page 24). Please consider the proposed for positioning for ripretinib to be in line with the NICE final scope, marketing authorisation and population included in the INVICTUS trial i.e. 4L+.	Please refer to response to comment #1 in this block. The text has been amended to clarify that the company’s intended positioning of ripretinib is as a 4L+ therapy. Figure 1 has not been amended as this is the company’s description of the pathway.
Page 23: “The company’s proposed positioning of ripretinib within the pathway is consistent with the final NICE scope and the marketing authorisation for ripretinib. However, the EAG notes that the company’s target population relates specifically to people who have received three prior therapies, i.e., the use of ripretinib at 4L, whereas more than one-third of patients in INVICTUS had received more than three prior therapies.”	“The company’s proposed positioning of ripretinib within the pathway (4L+) is consistent with the final NICE scope and the marketing authorisation for ripretinib and the patient population of INVICTUS.” Add SmpC reference.	Company positioning was communicated too narrowly in the CS (Section 1.4.2, page 24). Please consider the proposed for positioning for ripretinib to be in line with the NICE final scope, marketing authorisation and population included in the INVICTUS trial i.e. 4L+.	Please refer to response to comment #1 in this block. The text highlighted in bold has been removed. A reference to the SmPC is not required as this is already included in the existing text.

Page 27: “The EAG notes that the company’s target population relates specifically to people who have received three prior TKIs, including imatinib. Section 1.4.2 of the CS (page 24) states that “It is therefore proposed that the place of ripretinib would be in the fourth-line of treatment, alongside BSC” (i.e., after imatinib, sunitinib and regorafenib). However, as noted in Section 2.2.2, more than one-third of patients in INVICTUS had received more than three prior therapies. As such, the company’s intended positioning of ripretinib as a 4L therapy means that the target population is a subgroup of the overall population covered by the EMA/MHRA licence and the clinical evidence from INVICTUS. However, the clinical evidence presented in the CS and the company’s economic model both reflect outcomes data for the intention-to-treat (ITT) population of INVICTUS, which includes patients who have received three or more prior therapies.”	~~“The EAG notes that the company’s target population relates specifically to people who have received three prior TKIs, including imatinib. Section 1.4.2 of the CS3 (page 24) states that “It is therefore proposed that the place of ripretinib would be in the fourth-line of treatment, alongside BSC” (i.e., after imatinib, sunitinib and regorafenib). However, as noted in Section 2.2.2, more than one-third of patients in INVICTUS2 had received more than three prior therapies. As such, The company’s intended positioning of ripretinib as a 4L+ therapy means that the target population is the overall population covered by the EMA/MHRA licence and the clinical evidence from INVICTUS.” However, the clinical evidence presented in the CS and the company’s economic model both reflect outcomes data for the intention-to-treat (ITT) population of INVICTUS, which includes patients who have received three or more prior therapies. Add SmpC reference.~~	Company positioning was communicated too narrowly in the CS (Section 1.4.2, page 24). Please consider the proposed for positioning for ripretinib to be in line with the NICE final scope, marketing authorisation and population included in the INVICTUS trial i.e. 4L+.	Please refer to response to comment #1 in this block. This paragraph has been removed as it is no longer necessary.

Page 29: "Section 1.5 of the CS states that there are no known equality issues relating to the use of ripretinib for treating advanced GIST after three therapies. "	"Section 1.5 of the CS states that there are no known equality issues relating to the use of ripretinib for treating advanced GIST after three or more therapies. " Add SmpC reference.	To be consistent with the final NICE scope of the appraisal.	The EAG agrees. The text has been amended as suggested.
Page 34: "The EAG notes that approximately one-third of patients in INVICTUS had received more than three prior therapies at enrolment (i.e., they were at fifth-line or later), whilst the company's intended positioning for ripretinib is specifically as a 4L therapy."	~~"The EAG notes that approximately one-third of patients in INVICTUS had received more than three prior therapies at enrolment (i.e., they were at fifth-line or later), whilst the company's intended positioning for ripretinib is as a 4L therapy aligns with the final NICE scope and SmpC for ripretinib."~~ Add SmpC reference.	Company positioning was communicated too narrowly in the CS (Section 1.4.2, page 24). Please consider the proposed for positioning for ripretinib to be in line with the NICE final scope, marketing authorisation and population included in the INVICTUS trial i.e. 4L+.	Please refer to response to comment #1 in this block. The text has been amended to only state the percentage of patients who had receive more than 4 prior lines of therapy in INVICTUS.
Page 41: "The EAG notes that approximately one-third of patients in INVICTUS had received more than three prior therapies, whilst the company's intended positioning for ripretinib is as 4L therapy (see CS, Section 1.4.2, page 23)."	Remove	Company positioning was communicated too narrowly in the CS (Section 1.4.2, page 24). Please consider the proposed for positioning for ripretinib to be in line with the NICE final scope, marketing authorisation and population included in the INVICTUS trial i.e. 4L+.	Please refer to response to comment #1 in this block. The text has been amended to remove reference to positioning of ripretinib as a 4L therapy.
Page 74: "However, there were some differences between INVICTUS and the company's proposed use of ripretinib. The	Remove	Company positioning was communicated too narrowly in the CS (Section 1.4.2, page 24). Please consider the proposed	Please refer to response to comment #1 in this block.

company's positioning of ripretinib is at 4L, whilst more than one-third of patients in INVICTUS had >3 prior therapies."		for positioning for ripretinib to be in line with the NICE final scope, marketing authorisation and population included in the INVICTUS trial i.e. 4L+.	This sentence has been removed.
Page 77, table 24: "Patients with advanced GIST after 3 therapies including imatinib, sunitinib and regorafenib. "	"Patients with advanced GIST after 3 or more therapies, including imatinib. " Add SmpC reference.	The economic model is aligned with the final NICE scope, marketing authorisation of ripretinib, INVICTUS patient population and ripretinib proposed positioning.	The EAG has amended the text as suggested.
Page 77: "The company's economic model assesses the cost-effectiveness of ripretinib (plus BSC) versus BSC alone for the treatment of patients with advanced GIST after at least three therapies, including imatinib, sunitinib and regorafenib. "	"The company's economic model assesses the cost-effectiveness of ripretinib (plus BSC) versus BSC alone for the treatment of patients with advanced GIST after at least three therapies, including imatinib. " Add SmpC reference.	The economic model is aligned with the final NICE scope, marketing authorisation of ripretinib, INVICTUS patient population and ripretinib proposed positioning.	The EAG has amended the text as suggested. The reference to the SmPC is unnecessary.
Page 78: "The company's economic analysis is intended to reflect the population of patients with advanced GIST who have received three prior therapies (i.e., the company intends to position ripretinib as 4L therapy)."	"The company's economic analysis is intended to reflect the population of patients with advanced GIST who have received three or more prior therapies (i.e., the company intends to position ripretinib as 4L+ therapy)." Add SmpC reference.	The economic model is aligned with the final NICE scope, marketing authorisation of ripretinib, INVICTUS patient population and proposed positioning of ripretinib.	The text has been amended as suggested. The latter half of the subsequent paragraph has been deleted.

Page 120: (2) Mismatch between anticipated positioning of ripretinib and evidence from INVICTUS	Remove paragraph	Company positioning was communicated too narrowly in the CS (Section 1.4.2, page 24). Please consider the proposed for positioning for ripretinib to be in line with the NICE final scope, marketing authorisation and population included in the INVICTUS trial i.e. 4L+.	Please refer to response to comment #1 in this block. This issue has been removed from the critical appraisal section.

Issue 2 Characterisation of the outputs of the advisory boards

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 17: [REDACTED]	[REDACTED]	Summary of the advisory board is too simplistic and does not capture the breadth of the responses from the clinicians.	The EAG believes that the company's proposed amendment is misleading - the estimate of [REDACTED] reflects the view of one clinician who referred to treatments improving and new options being developed (i.e., not the current pathway including ripretinib). All other estimates provided by the clinicians at the advisory board meeting were markedly lower than [REDACTED]. For clarity, the text has been amended to read "The minutes of the company's 2024 advisory board

			meeting suggest that overall, the clinical advisors considered that a model-predicted probability of OS of ■ at 10 years was an overestimate and a probability of ■ was more realistic. One advisor commented that ■ OS at 10 years is plausible because treatments are improving and new options are being developed; however, this advisor's view does not relate to expected OS if ripretinib was added to the current treatment pathway for GIST."
Page 17: "The EAG's preferred analysis uses the log-logistic model fitted to these adjusted data because it gives a predicted probability of 10-year OS for ripretinib ■ ■ provided by the clinical experts at the company's advisory board meeting."	"The EAG's preferred analysis uses the log-logistic model fitted to these adjusted data because it gives a predicted probability of 10-year OS for ripretinib of ■ ■ deemed plausible by the clinical experts at the company's advisory board meeting."	Summary of the advisory board is too simplistic and does not capture the breadth of the responses from the clinicians.	The EAG believes that including the range of estimates is somewhat misleading because the clinician who gave an OS estimate of ■ was not referring to predicted OS if ripretinib was added to the current treatment pathway. The text has been amended to include "deemed plausible" as suggested.

Page 129, table 45: “Model prediction of 10-year OS is closest to the overall estimate of █████ suggested by company’s advisors.”	“Model prediction of 10-year OS is closest to the overall average estimate of █████ suggested by company’s advisors.”	Language could be interpreted as all advisors agreed with █████ whereas there was actually a range of opinions.	This is not a factual inaccuracy. It is not clear from the advisory board meeting minutes that the estimate of █████ is an average. The text has not been amended.
Page 91: “The CS states that clinical advisors consulted by the company considered the exponential distribution to be the most appropriate model based on consideration of the modelled hazards.”	“The CS states that clinical advisors consulted by the company considered the exponential distribution to be the most appropriate model based on consideration of the modelled hazards and clinical plausibility. ”	Clinical advisors state in the 2025 advisory board report that the ‘time-on-treatment’ curve used in the economic model was clinically plausible (page 11).	The EAG agrees. The text has been amended to include “and clinical plausibility.”
Page 126: “ it appears that the company has selected a base case OS distribution which was deemed to be clinically implausible by most of the clinical experts who attended the 2024 advisory board meeting.”	~~“it appears that~~ the company has selected a base case OS distribution which was outside the 10-year survival estimates given by most of the clinical experts who attended the 2024 advisory board meeting.”	The clinical advisors in the 2024 advisory board did not state that the log-logistic curve was ‘clinically implausible.’ Suggested language aligns with the advisory board report.	The EAG has amended to wording as follows: “Based on the advisory board meeting minutes and the company’s clarification response, the company has selected a base case OS distribution which produces substantially more optimistic predictions of OS than the expected OS estimates suggested by most of the clinical experts who attended the 2024 advisory board meeting.”

Page 127, table 44: “ Based on AIC (EAG note: the generalised gamma model does not have the lowest AIC in either treatment group).”	“ Based on AIC (one of the lowest) and best visual fit (EAG note: the generalised gamma model does not have the lowest AIC in either treatment group).”	To align accurately with the advisory board report (page 9).	The EAG disagrees. The generalised gamma model has the fourth lowest combined AIC. The text has been amended to read: “(EAG note: the generalised gamma model has the fourth lowest combined AIC value).”
Page 129: “the selection of the log-logistic model for the ripretinib group which produces predictions of OS which were considered to be implausibly optimistic by the EAG’s clinical advisors and most of the clinical experts consulted by the company at the 2024 advisory board meeting.”	“the selection of the log-logistic model for the ripretinib group which produces predictions of OS which were considered to be implausibly optimistic by the EAG’s clinical advisors and above the predictions given by most of the clinical experts consulted by the company at the 2024 advisory board meeting.”	The clinical advisors in the 2024 advisory board did not state that the log-logistic curve was ‘implausible.’ Suggested language aligns with the advisory board report.	The text has been amended to read “the selection of the log-logistic model for the ripretinib group which produces predictions of OS which were considered to be implausibly optimistic by the EAG’s clinical advisors and which are higher than estimates of expected 10-year OS provided by most of the clinical experts consulted at the company’s 2024 advisory board meeting.”
Page 134: “... generates a predicted probability of 10-year OS consistent with estimates provided by the	“... generates a predicted probability of 10-year OS consistent with estimates provided by most of the clinical advisors consulted by the company and the EAG.”	Advisors gave a range of estimates, some higher than the one predicted by the model referred to here.	The text has been amended to read “generates a predicted probability of 10-year OS consistent with estimates provided by the EAG’s clinical advisors and

clinical advisors consulted by the company and the EAG.”			most of the clinical advisors consulted by the company.”
Page 147: “The clinical experts who attended the company’s 2024 advisory board meeting stated that x [REDACTED]	“The clinical experts who attended the company’s 2024 advisory board meeting stated that [REDACTED]	Summary of the advisory board is too simplistic and does not capture the breadth of the responses from the clinicians.	The text has been amended to read: “The clinical experts who attended the company’s 2024 advisory board meeting stated that a predicted probability of OS at 10 years for ripretinib of [REDACTED] was an overestimate and that [REDACTED] was more realistic. One clinician considered that an estimate of [REDACTED] was plausible because treatments are improving and new options are being developed; however, the EAG notes that this expert’s estimate does not reflect expected OS if ripretinib was included in the current treatment pathway for GIST.”

Issue 3 Objective language

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 14: “...this indicates that continued post-progression	“...this indicates that continued post-progression regorafenib may be	Proposed amendment is the language used later in the report (Section 2.3.3, p29). This	The EAG agrees. The text has been amended as suggested.

regorafenib is a relevant comparator for ripretinib.”	considered as a relevant comparator for ripretinib.”	is preferred as post-progression regorafenib as a relevant comparator is subjective.	
Page 17: “The visual fit of the OS models in the ripretinib group is poor.”	“The visual fit of the OS models in the ripretinib group is considered poor.”	Whether the fit of the OS models is poor is subjective; the proposed amendment reflects this.	The EAG disagrees. The fit of the models is poor. The report has not been amended.
Page 86: “Nevertheless, since patients were not randomised to receive BID, this analysis is biased due to informative censoring and does not reflect a fair comparison.”	“Nevertheless, since patients were not randomised to receive BID, this analysis is likely biased due to informative censoring and does not reflect a fair comparison.”	The analysis cannot definitely be considered biased, but there is a likelihood due to the reasons listed.	The EAG agrees. The text has been amended as suggested.
Page 123/124: “However, the overall visual fit of the models to the ripretinib OS data is poor .”	“However, the overall visual fit of the models to the ripretinib OS data may be considered poor .”	Whether the fit of the OS models is poor is subjective; the proposed amendment reflects this.	The EAG disagrees. The fit of the models is poor. The report has not been amended.
Page 125: “The CS for the current appraisal refers briefly to considerations of the clinical plausibility,…”	“The CS for the current appraisal refers briefly to considerations of the clinical plausibility,…”	‘Briefly’ is subjective and does not aid the interpretation of the data.	The EAG has amended the text to read: “The CS for the current appraisal ³ provides some, albeit limited, discussion regarding considerations of the clinical plausibility.”
Page 86: “However, as patients were not randomised to dose escalation, selecting subgroups	“However, as patients were not randomised to dose escalation, selecting subgroups based on post-randomisation	Although the analysis is likely subject to bias due to the non-randomised nature of the	The text has been amended to read: “However, as patients were

based on post-randomisation characteristics introduces selection bias, and therefore no causal interpretation of the effect of dose escalation can be drawn from these comparisons. Specifically, attrition bias is apparent, as the proportion of non-progressors in each of these analyses would not reflect the natural rate of progression and non-progression in the overall population.”	characteristics introduces selection bias, and therefore limited causal interpretation of the effect of dose escalation can be drawn from these comparisons. Specifically, attrition bias is apparent, as the proportion of non-progressors in each of these analyses would not reflect the natural rate of progression and non-progression in the overall population.”	subgroups, the analysis is still likely to support the interpretation of the effect of BID, in context, and together with other analyses.	not randomised to dose escalation, selecting subgroups based on post-randomisation characteristics introduces selection bias. In particular, attrition bias is apparent: the proportion of non-progressors in each of these analyses would not reflect the natural rate of progression and non-progression in the overall population. Consequently, these comparisons do not allow for reliable inferences about the causal effect of dose escalation.”
Page 121: “The exclusion of these additional data from the model is a limitation which unnecessarily increases uncertainty around the effect of ripretinib on OS. Specifically, an additional year of follow-up would better characterise the tail of the survival distribution which could help to inform parametric survival model selection.”	“The exclusion of these additional data from the model is a limitation which may unnecessarily increase uncertainty around the effect of ripretinib on OS. Specifically, an additional year of follow-up may better characterise the tail of the survival distribution which could help to inform parametric survival model selection. However, it is important to note, use of the 2022 DCO may increase the risk of bias and confounding. Moving further into the post-unblinding, post-treatment	Conclusion is too simplistic and does not consider the characteristics of this particular data.	The relevant paragraph has been amended to read: “The EAG considers that, despite the limitations of follow-up during the unblinded period, long-term follow-up data would provide valuable insights. In particular, such data could help clarify the trajectory of longer-term hazard ratios and hazard shapes, both of which are

	switch/IPDE period increases the potential risk due to informative drop-out and other biases associated with data collection in the open-label setting.”		important considerations for survival extrapolation. Specifically, an additional year of follow-up would better characterise the tail of the survival distribution which could help to inform parametric survival model selection. Intercurrent events such as IPDE in the experimental arm and treatment crossover in the control arm complicate interpretation of the ITT analysis. However, the company has attempted to address these issues using the two-stage adjustment method (Section 4.2.4), which the EAG deems reasonable. With longer follow-up, more patients are expected to progress, increasing the effective sample size for both IPDE and crossover adjustments. This would likely allow for more reliable estimates, provided potential biases

			are appropriately accounted for through the chosen covariates – which the EAG’s clinical advisors considered reasonable – and characterisation of longer-term treatment effects. In line with TSD24 guidance,⁴⁷ which recommends presenting two-stage adjustment results both with and without re-censoring, longer-term data would be especially valuable to mitigate information loss in the re-censoring scenarios (i.e., EAG’s preferred scenarios for addressing treatment switching in the control arm and IPDE in the ripretinib arm). Although outcome measurement could be affected by the open-label nature of the follow-up data, the EAG notes that OS is a hard endpoint and therefore less susceptible to subjective influences.

			While the company has stated concerns regarding the open-label nature of the data at the fact check stage of the appraisal, the EAG's considers that the benefits of examining longer-term follow-up outweigh the risks. Excluding these data would constrain the understanding of longer-term survival outcomes and may increase decision uncertainty. Given the absence of alternative evidence on longer-term ripretinib use, the EAG considered that including the long-term data provides a more balanced basis for decision-making."

Issue 4 Inferences regarding company decision-making

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 86: "The EAG suspects this choice reflects the company's use of log-logistic models as in its preferred base case with unadjusted ripretinib OS, or because the	"This choice reflects the company's use of log-logistic models as in its preferred base case with unadjusted ripretinib OS, and because the log-logistic models showed the lowest combined AIC values for the IPDE-adjusted ripretinib OS (CS, Table	The company confirms these are the main reasons.	The EAG agrees. The text has been amended as suggested.

log-logistic models showed the lowest combined AIC values for the IPDE-adjusted ripretinib OS (CS, Table 34) and placebo OS (with two-stage adjustment) (CS, Table 33)."	34) and placebo OS (with two-stage adjustment) (CS, Table 33)."		
Page 130: "as well as an additional scenario analysis in which the costs of BID dosing are included for 50% of patients' post-progression ripretinib treatment time (see Table 41, Scenario S36)."	"as well as an additional scenario analysis in which the costs of BID dosing are included for 50% of patients who continue ripretinib post-progression (estimate elicited from clinical advisors in the 2025 advisory board) (see Table 41, Scenario S36)."	The company's assumption for this scenario was that ~50% of the patients continuing ripretinib post-progression would dose escalate rather than assuming that 50% of post-progression time would be spent on BID.	This parameter is applied to the proportion of patients in the PDon state in each cycle. This is equivalent to determining the proportion of the post-progression on treatment time spent on the BID dose. The report has not been amended.
Page 130: "The company's response states that 60.1% of post-progression ripretinib exposure time was spent receiving BID dosing; this estimate is 10.1% higher than the proportion applied in Scenario S36."	"The company's response states that 60.1% of post-progression ripretinib exposure time was spent receiving BID dosing; this estimate is 10.1% higher than the proportion applied in Scenario S36 where the company considered proportion of patients on BID rather than time on BID. "	The company's assumption for this scenario was that ~50% of the patients continuing ripretinib post-progression would dose escalate rather than assuming that 50% of post-progression time would be spent on BID. The assumption of ~50% was elicited during the 2025 advisory board.	Given that the model does not distinguish between treatment time spent on the QD and BID dose, assuming that 50% of patients receive BID dosing is equivalent to assuming that 50% of post-progression treatment time is spent on the BID dose. The report has not been amended.

Issue 5 Ambiguous language

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 14: "...more than one-third of patients in INVICTUS had received more than three prior therapies." This is repeated on pages 15, 23, 27, 74, 78	"...more than one-third (37%) of patients in INVICTUS had received more than three prior therapies."	Language considered ambiguous as referring to 'more than one third' is very broad.	The EAG agrees. The text has been amended.
Page 21: "As the clinical evidence for this appraisal remains unchanged from TA881 ..."	"As the clinical evidence informing the economic model for this appraisal remains unchanged from TA881 ..."	Data informing the model has not changed but the appraisal included new data from the Royal Marsden observational study.	The EAG agrees. The text has been amended as suggested.
Page 28: "The final NICE scope includes a single comparator - established clinical management. The INVICTUS trial was placebo-controlled, and the comparator considered in the CS and the company's economic model is BSC alone."	"The final NICE scope includes a single comparator - established clinical management. The INVICTUS trial was placebo-controlled (BSC + placebo), and the comparator considered in the CS and the company's economic model is BSC alone.	Clarity as sentence currently could be misinterpreted as BSC not being included in the placebo arm of INVICTUS.	The EAG agrees. The text has been amended to reflect this point.
Page 73: "The electronic search strategy was inadequate for finding all the included studies described in CS SLR; however, it	"The electronic search strategy was inadequate for finding all the included studies described in CS SLR; however, given the company's supplementary	Language presents as contradictory. Suggest to add the	The EAG agrees. The text has been amended as suggested.

is unlikely that any relevant studies have been missed.”	searches , it is unlikely that any relevant studies have been missed.”	language used earlier in the report on page 31.	
Page 74: “HRQoL was only reported for both groups during the first cycle (the first 29 days) ...”	“HRQoL was only reported for both groups during the first cycle (the first 29 days, due to attrition in the placebo arm, patient numbers were low after this point) ...”	Language could imply a lack of transparency from the company when the reason for not reporting the data was due to attrition in the placebo arm.	The EAG agrees. The text has been amended as suggested.
Page 79: “Patients in the ripretinib group are assumed to receive treatment during the entire PFS period and during part of the post-progression survival period.”	“Patients in the ripretinib group are assumed to receive treatment during the entire PFS period and during part of the post-progression survival period (this is governed by the PFS+TTD curve) .”	Addition suggested for clarity on the economic model.	The EAG does not consider the existing text to be inaccurate and the use of PFS+TTD is already described on pages 82 and 91.
Page 80: “This aspect of the model is subject to an error (see Section 5.3.5, critical appraisal point 1).”	“This aspect of the model is subject to an error (see Section 5.3.5, critical appraisal point 1); however, this was corrected in the clarification response B24. ”	Language could imply that the company did not correct this when requested.	The EAG disagrees. The company’s revised model is described in Section 4.3.5, page 119. For the sake of clarity, the introductory text on page 75 has been amended to read: “Section 4.2 describes the original version of the company’s economic model and summarises its results.”
Page 80: “... although this part of the model is also subject to an	“... although this part of the model is also subject to an error (see Section 4.3.5, critical appraisal point 1);	Language could imply that the company did not correct this when requested.	Please refer to response above.

error (see Section 4.3.5, critical appraisal point 1)."	however, this was corrected in the clarification response B23."		
Page 81: "The model includes a structural constraint which should prevent the mortality risk for people with advanced GIST from being lower than that for the age- and sex-matched general population (although this has been implemented incorrectly ; see Section 4.3.5)."	"The model includes a structural constraint which should prevent the mortality risk for people with advanced GIST from being lower than that for the age- and sex-matched general population (although this was initially implemented incorrectly, it was corrected in the clarification response B24 ; see Section 4.3.5)."	Language could imply that the company did not correct this when requested.	Please refer to response above.
Page 81: "AEs result in QALY losses and additional costs. The CS indicates that AEs are assumed to be resolved within the first 28-day model cycle (although the model is subject to an error whereby AE-related QALY losses are applied in all cycles)."	"AEs result in QALY losses and additional costs. The CS indicates that AEs are assumed to be resolved within the first 28-day model cycle (although the model was initially subject to an error whereby AE-related QALY losses are applied in all cycles, this was corrected in the clarification response B23)."	Language could imply that the company did not correct this when requested.	Please refer to response above.
Page 86: "In Approach 2(b), the company compared OS between two non-mutually exclusive subgroups: (i) patients with progressed disease who escalated to BID dosing combined with those who did not progress versus (ii) patients who progressed who did not	"In Approach 2(b), the company compared OS between two non-mutually exclusive subgroups: (i) patients with progressed disease who escalated to BID dosing combined with those whose disease did not progress versus (ii) patients with progressed disease who did not escalate to BID dosing combined with	Consistency in language to ensure clarity of interpretation, as well as patient-centric terminology.	The EAG agrees. The text has been amended as suggested.

escalate to BID dosing combined with non-progressors.”	those whose disease did not progress.”		
Page 101: “The disutility value for abdominal pain was based on an EQ-5D VAS estimate for pain in people with lung cancer reported by Doyle et al. The CS states that the disutility for hypertension was also taken from Doyle et al., although the EAG notes that this study does not report values for this type of AE; it appears that the company has assumed that the disutility for hypertension is equivalent to that for pain . Whilst this assumption has been applied in previous appraisals (e.g., NICE TA439), the justification for assuming hypertension and pain have equivalent HRQoL impacts is unclear.”	“The disutility value for abdominal pain was based on an EQ-5D VAS estimate for chest pain in people with lung cancer reported by Doyle et al. The CS states that the disutility for hypertension was also taken from Doyle et al., although the EAG notes that this study does not report values for this type of AE; it appears that the company has assumed that the disutility for hypertension is equivalent to that for chest pain . Whilst this assumption has been applied in previous appraisals (e.g., NICE TA439), the justification for assuming hypertension and chest pain have equivalent HRQoL impacts is unclear.”	Added clarity on type of pain otherwise the relevance to a hypertension disutility is unclear.	The EAG agrees. The text has been amended to instead refer to chest pain.
Page 101: “Based on the description of the model in the CS, the company had intended to apply AE-related QALY losses in in the first model cycle based on an assumed duration of 28 days; however, the model is subject to an error whereby the QALY loss is applied in every model	“Based on the description of the model in the CS, the company had intended to apply AE-related QALY losses in in the first model cycle based on an assumed duration of 28 days; however, the model was initially subject to an error whereby some QALY losses were applied in every model cycle; however this was	Language could imply that the company did not correct this when requested and also states the error to be greater than it was.	Please refer to response above.

cycle (see Section 4.3.5, critical appraisal point 1)."	corrected in the clarification response B23 (see Section 4.3.5, critical appraisal point 1)."		
Page 105: "The currency codes shown in the table reflect those reported in the CS; however, the EAG notes that some of these appear to be inaccurate."	"The currency codes shown in the table reflect those reported in the CS." Or EAG to specify which codes were inaccurate.	The sentence lacks clarity and requires more information to be meaningful to the report. If nothing can be added, suggest to remove to avoid misinterpretation.	Some of the cost codes included in the tables of the CS reflect a different coding system compared to that used in the most recent version of the NHS Cost Collection (for example DAPS04 and DAPS04 in the previous version). This likely reflects a series of minor reporting errors in the CS which have not been updated since the earlier appraisal. The EAG report retains the codes as reported in the current CS, but highlights that some of these do not appear to be accurate. No further additional text is required.
Page 108: "All results include the proposed PAS for ripretinib and a decision modifier of 1.7 (unless otherwise stated)."	"All ICERs include the proposed PAS for ripretinib and a decision modifier of 1.7 (unless otherwise stated)."	Misleading as the text and table immediately below include LYG and QALYs without the modifier applied and without stating this in the text or table. This	The EAG agrees. The text has been amended throughout the report.

		continues throughout the section.	
Page 129, table 45: "Model does not reflect shape of empirical hazard."	Add more context to the sentence and align with either the unadjusted or adjusted choice in the table.	Unclear what this is referring to in the table and how it justifies the EAGs preferred model.	The EAG agrees. The text has been amended from "Model does not" to "Modelled hazard does not"
Page 129, table 45: "The EAG notes that this is a different distribution compared with that selected for the ripretinib group."	Add an explanation of the implications of having a different distribution.	Unclear what the impact of this is on the model and why the EAG has included this.	This reflects an observation that the Appraisal Committee may wish to consider in its deliberations. Further discussion of the implications of selecting different survival distributions between the treatment groups is not necessary.
Page 132: "This model's hazard function closely aligned with the smoothed empirical hazard (see Figure 35), and the extrapolation projected a 10-year survival that was similar to (but slightly lower than) that of the unadjusted OS. "	Further context required.	It is unclear what this sentence is referring to and how it should be interpreted.	The EAG is unclear what requires further context. The text refers to an observation that the log-logistic distribution fitted to the BID-adjusted ripretinib OS data provides a similar OS estimate to the unadjusted ripretinib OS data. The text has been amended slightly to clarify

			what the unadjusted OS model relates to.
Page 134: “The EAG notes that the re-censoring scenario with the complex generalised gamma model for time ratio estimation and the log-logistic model for survival extrapolation generates a predicted probability of 10-year OS consistent with estimates provided by the clinical advisors consulted by the company and the EAG.”	“The EAG notes that the re-censoring scenario with the complex generalised gamma model for time ratio estimation and the log-logistic model for survival extrapolation generates a predicted probability of 10-year OS consistent with estimates provided by the clinical advisors consulted by the company and the EAG. The without re-censoring scenario generates a higher predicted probability of 10-year OS, but still within the range of the estimates provided by the clinical advisors consulted by the company, when using log-logistic, lognormal or generalised gamma to model survival extrapolation. ”	Omits the assessment of the without re-censoring scenario. Our understanding is that this scenario generates predicted probabilities of 10-year OS still within the range of those elicited from the 2024 advisory board.	The EAG has included the following additional text to the end of the quoted text: “The without re-censoring scenario generates a higher predicted probability of 10-year OS for all six parametric survival models compared to their equivalent models including re-censoring.”

Issue 6 Minor typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 21: “...relates to the company’s proposed used of ripretinib”	“...relates to the company’s proposed use of ripretinib”	Minor typographical error.	The EAG agrees. The text has been amended as suggested.
Page 109, table 40: “LYGs*”, “Inc. LYGs*”	“LYGs”, “Inc. LYGs” (remove asterisks)	No corresponding footnote.	The EAG agrees. The footnote has been amended to state that LYGs are undiscounted”

Issue 7 Data and omission errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 14: “The most common Grade 3/4 treatment-emergent adverse events (TEAEs) with ripretinib (vs. placebo) were: anaemia (11% vs. 14%); abdominal pain (7% vs. 5%); hypertension (7% vs. 0%); increased lipase (5% vs. 0%) and hypophosphataemia (5% vs. 0%). Treatment-related Grade 3/4 TEAEs were reported in 25% of patients in the ripretinib arm and 16% of patients in the placebo arm.”	“At the January 2021 DCO, the most common Grade 3/4 treatment-emergent adverse events (TEAEs) with ripretinib (vs. placebo) were: anaemia (11% vs. 14%); abdominal pain (7% vs. 5%); hypertension (7% vs. 0%); increased lipase (5% vs. 0%) and hypophosphataemia (5% vs. 0%). At the May 2019 DCO, treatment-related Grade 3/4 TEAEs were reported in 25% of patients in the ripretinib arm and 16% of patients in the placebo arm.”	The paragraph starts with ‘At the May 2019 data cut-off (DCO),’ however, the Grade 3/4 TEAE data is from the January 2021 DCO.	The EAG agrees. The text has been amended as suggested.
Page 19: “... whether the BID-adjustment of OS includes re-censoring; whether the BSC OS data are adjusted for treatment switching and the choice of parametric survival model selected for TTD.” Repeated on page 79, 80, 81, 87, 90, 99, 103, 111, 124, 128, 129, 137, 139, 141, 148 and table 2, 41, 45 and 50	“... whether the BID-adjustment of OS includes re-censoring; whether the BSC OS data are adjusted for treatment switching and the choice of parametric survival model selected for PFS+TTD.”	The economic model included data from the composite endpoint PFS+TTD; TTD data alone was not used in the model.	The EAG disagrees. As explained in the EAG report, the model uses data on PFS+TTD as a composite end point; however, this is used to reflect time spent on treatment (i.e., TTD) in the economic model. The EAG considers that the company’s proposed amendment is likely to introduce confusion; the report has not been amended.

Page 20, Table 2: “ASA6a: Unadjusted 0.29 - £77,120 - £219,436 - 1.2 - £166,614 ”	“ASA6a: Unadjusted - 0.29 - £77,120 - £154,896 - 1.7 - £102,074 ”	The EAG amended model does not align with the EAG report regarding ASA6a, this due to a 1.2 DM being applied in the report and a 1.7 DM applied in the model. The report or model should therefore be adjusted so there is alignment.	The ICER for ASA6a presented in the EAG report reflects a decision modifier of 1.2, which reflects the appropriate modifier given the expected QALYs in the comparator group for this scenario. The EAG report has not been amended.
Page 28: “The CS states that additional testing is required for people prior to and during treatment with ripretinib. This includes: (i) monitoring for people with a history of high blood pressure which may require blood pressure medication ...”	“The CS states that additional testing is required for people prior to and during treatment with ripretinib. This includes: (i) monitoring for people with a history of high blood pressure which may require blood pressure medication, as clinically indicated ...”	Language updated to reflect SmPC.	The text has been amended as suggested.
Page 29: “The company’s economic model is informed by data on PFS, OS, adverse events (AEs) and HRQoL from INVICTUS (see Section 3.2.4).”	“The company’s economic model is informed by data on PFS, TTD , OS, adverse events (AEs) and HRQoL from INVICTUS (see Section 3.2.4).”	TTD was used to create the composite endpoint of PFS and treatment discontinuation (PFS+TTD) which was included in the model.	The EAG agrees. The text has been amended as suggested.
Page 30: “The company performed an initial SLR in July 2020 followed by four	“The company performed an initial SLR in July 2020, followed by five updates in July	Additional SLR update performed in May 2023.	The text has been amended as

updates in July 2021, March 2022, April 2024 and March 2025 (CS, Appendix D)." Repeated on page 75	2021, March 2022, May 2023 , April 2024 and March 2025 (CS, Section 2.1) (CS, Appendix B)."	Details found in CS, Section 2.1, page 26 or appendix B.	suggested. Note that CS Appendix B does not mention the May 2023 update.
Page 33: "Response rates"	"Response rates (including partial response rate and duration of response)"	To align with Table 3 of the report (page 25).	The EAG agrees. The text has been amended as suggested.
Page 39: "As of January 2021, 63 of 85 patients (76%) originally randomised to ripretinib had entered the open-label period following disease progression based on independent radiological review."	"As of January 2021, 63 of 85 patients (74%) originally randomised to ripretinib had entered the open-label period following disease progression based on independent radiological review."	Calculation error.	The EAG agrees. The text has been amended as suggested.
Page 39: "However, the EAG identified a discrepancy between these figures and those relating to the August 2020 DCO... Nonetheless, the EAG remains cautious in its interpretation."	"By the January 2021 DCO, of the 71 events, 65 patients had progressed in the ripretinib arm, and 63 (59 with progression, 4 without progression) had entered the open-label period (44 dose-escalated and 19 remained on QD). As such, 6 patients in the ripretinib group who progressed did not enter the open-label period. For clarification response A3, the number of patients who entered the open-label phase was recalculated based on the PFS statistical analysis plan (SAP) rule and subsequent treatment received. Of the 63 in the patient disposition 2021 DCO DOF, 4	The data for clarification response A3 cannot be directly combined with the disposition tables for INVICTUS as the rules for the classification of patients was different for A3. This was because the A3 request was "Please provide information on the duration of post-progression ripretinib treatment at each dose (mean, standard deviation	Additional text has been added to Section 3.2.2. to reflect this additional information. However, the EAG cannot verify the company's interpretation given inconsistent terminology between the CS, the clarification

	patients censored in the PFS analysis but who entered the open-label phase were not included taking the number down to 59. Subsequently, 6 patients who progressed but did not enter the open-label phase were included, taking the number up to 65.”	and range).” Accordingly, the analysis conducted was restricted to post-progression ripretinib exposure in subjects with BICR-confirmed progression. This is not the same as ripretinib exposure during open-label period, due to some subjects entering the open-label period prior to BICR-confirmed progression.	response, this FAC response form and the INVICTUS protocol.
Page 40: “Based on the definition provided, the EAG considers that the “QD only group” in Table 6 may have included the six patients who progressed but did not enter the open-label phase. As these six patients should not have received further treatment, their post-progression duration would be zero, potentially lowering the mean for the QD only group.”	“Based on the definition provided, the EAG considers that the “QD only group” in Table 6 ~~may have~~ included the six patients who progressed (BICR-confirmed) but did not enter the open-label phase. As such, these patients may or may not have received post-progression treatment with ripretinib as the purpose of the analysis was to quantify post-progression ripretinib exposure in subjects with BICR-confirmed progression ~~As these six patients should not have received further treatment, their post-progression duration would be zero, potentially lowering the mean for the QD only group.”~~	The analysis presented in Table 6 was restricted to post-progression ripretinib exposure in subjects with BICR-confirmed progression. This is not the same as ripretinib exposure during open-label period, due to some subjects entering the open-label period prior to BICR-confirmed progression.	The text has been amended to read: “Based on the definition provided, the EAG considers that the “QD only group” in Table 6 included the six patients who progressed (BICR-confirmed) but did not enter the open-label phase. Thus, the duration of post-progression ripretinib treatment for patients labelled as “QD only” label

			should be interpreted with caution, as it contains six patients with post-progression duration of zero, lowering the group mean.”
Page 40: “The number of patients in the QD only vs. BID groups in Table 6 also appears to be slightly inconsistent with earlier figures reported for this DCO (19 received post-progression QD; 44 received post-progression BID).”	“The number of patients in the QD only vs BID groups differs from earlier figures (19 received post-progression QD; 44 received post-progression BID). However, again, this is due to the definition of patients included in Table 6 as all patients who had progression according to the PFS rules in the SAP. As such, as one of the 19 did not have progression, as defined by the SAP, but progressed to open label QD nevertheless. In addition to these 18 who progressed and went to open label QD, the 6 patients mentioned earlier who progressed but did not go to open label QD (discontinued) are also included in the QD only group, giving 24 patients. Also, the 41 patients quoted in Table 6 differs from the 44 received post-progression BID, as there were 3 patients who underwent IPDE to BID who had no progression as defined by the SAP.”	Language updated to reduce uncertainty. The analysis presented in Table 6 was restricted to post-progression ripretinib exposure in subjects with BICR-confirmed progression. In addition, the PFS rules from the SAP were applied. This is not the same as ripretinib exposure during open-label period, due to some subjects entering the open-label period prior to BICR-confirmed progression.	The text has been amended as follows: “The number of patients in the QD only vs. BID groups in Table 6 also appears to be slightly different with earlier figures reported for this DCO in the CS (19 received post-progression QD; 44 received post-progression BID). At the FAC stage of the appraisal, the company explained that the values reported in Table 6 were derived from

			the definition of BICR-confirmed progression used in clarification question A3, and were therefore slightly different, as described earlier..”
Page 53: “The CS included data only from the May 2019 DCO; data from subsequent cut-offs were not provided. ”	Suggest to remove sentence and instead add reference to the correct data cut for TTP as has been included for the other secondary endpoints: “At the May 2019 DCO, median TTP was longer in the ripretinib group than the placebo group ...”	Data from the Jan 2021 data cut was provided in the CS and referenced in the text further down page 53 in the report for the other secondary endpoints where available.	The EAG agrees. The sentence has been removed. The DCO for TTP has been amended.
Page 77: “The EAG is unsure why this study has not been discussed in the CS, as it appears to be directly relevant to the decision problem.”	Remove sentence	Liao et al is discussed in the CS 3.2, page 103.	The EAG agrees. The sentence has been removed.
Page 79: “The probability of being on treatment following disease progression is calculated as the cumulative probability of TTD minus the cumulative probability of PFS (this applies to the ripretinib group only);”	“The probability of being on treatment following disease progression is calculated as the cumulative probability of having progressed and discontinued treatment, minus the cumulative probability of PFS (this applies to the ripretinib group only);”	Incorrect characterisation of the economic model.	The EAG agrees. The text has been amended as suggested.

Page 83: “The decision to remain on ripretinib (at either the current or increased dose) was informed by the investigator’s view of whether the patient was obtaining benefit from ripretinib, and if dose escalation could be tolerated.”	“The decision to remain on ripretinib (at either the current or increased dose) was informed by the investigator’s view of whether the patient was obtaining benefit from ripretinib, if dose escalation could be tolerated and whether or not they had access to additional therapies. ”	Accuracy regarding choice to dose escalate.	The EAG has included this additional detail.
Page 89: “Second, the company inappropriately applied a uniform time ratio adjustment to all patients who had progressed at each time point , rather than restricting it to those who actually underwent dose escalation.”	“Second, the company inappropriately applied a uniform time ratio adjustment to all patients who had progressed and remained on treatment at each time point , rather than restricting it to those who actually underwent dose escalation.”	Point of accuracy regarding the analysis.	The EAG disagrees. The formula does not incorporate the proportion of patients receiving treatment at each time point among those who had progressed. This is why the company was asked to re-do the analysis in B9. The text was amended to read: “Second, the company inappropriately applied a uniform time ratio adjustment to all patients who had progressed at each time point in the

			model, rather than restricting it to those who actually underwent dose escalation. This application is inconsistent with the derivation of the time ratio, which was based on patients who had progressed and remained on treatment at each time point.”																																					
Page 96: “When combined (based on the sum of the AIC/BIC across both groups), the log-logistic model had the lowest AIC, whereas the exponential model had the lowest BIC. The company selected the log-logistic distribution for inclusion in the base case model.” [Table 28, Generalised Gamma, Combined, AIC, BIC] <table><tr><th rowspan="2">Distribution</th><th colspan="2">Combined</th></tr><tr><th>AIC</th><th>BIC</th></tr><tr><td>Exponential</td><td>591.95</td><td>596.17</td></tr><tr><td>Weibull</td><td>592.66</td><td>601.11</td></tr><tr><td>Gompertz</td><td>594.13</td><td>602.58</td></tr><tr><td>Log-logistic</td><td>589.94</td><td>598.40</td></tr></table>	Distribution	Combined		AIC	BIC	Exponential	591.95	596.17	Weibull	592.66	601.11	Gompertz	594.13	602.58	Log-logistic	589.94	598.40	“When combined (based on the sum of the AIC/BIC across both groups), the log-logistic model had the lowest AIC and BIC. The company selected the log-logistic distribution for inclusion in the base case model.” [Table 28, Generalised Gamma, Combined, AIC, BIC] <table><tr><th rowspan="2">Distribution</th><th colspan="2">Combined</th></tr><tr><th>AIC</th><th>BIC</th></tr><tr><td>Exponential</td><td>552.55</td><td>556.78</td></tr><tr><td>Weibull</td><td>551.64</td><td>560.10</td></tr><tr><td>Gompertz</td><td>553.90</td><td>562.35</td></tr><tr><td>Log-logistic</td><td>547.38</td><td>555.83</td></tr><tr><td>Log-normal</td><td>548.63</td><td>557.09</td></tr></table>	Distribution	Combined		AIC	BIC	Exponential	552.55	556.78	Weibull	551.64	560.10	Gompertz	553.90	562.35	Log-logistic	547.38	555.83	Log-normal	548.63	557.09	AIC and BIC statistics for the combined group were incorrectly copied from the CS (Table 33).	The EAG agrees. The values have been replaced with those included in this FAC form. The text has been amended to state that the log-logistic model has the lowest combined AIC and combined BIC.
Distribution		Combined																																						
	AIC	BIC																																						
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Page 103: “Where a range of doses was available, the CS states that the lowest price for each medication was used; however, the EAG notes that this is not accurate as lower prices are available for several products in the Commercial Medicines Unit (CMU) electronic Market Information Tool (eMIT).”	“Where a range of doses was available, the CS states that the lowest price for each medication was used, sourced either from the Commercial Medicines Unit (CMU) electronic Market Information Tool (eMIT) or the BNF ; however, the EAG notes that this is not accurate as lower prices are available for several products in the CMU eMIT .”	Medication costs were also sourced from the BNF and, for a couple of the medicines in question, the lowest values from the BNF were used.	The CS only describes using the BNF – eMIT is not mentioned. This was amended in response to clarification questions from the EAG; however, some of the updated costs still did not reflect the lowest prices from either the BNF or the CMU. The text does not require amendment.									
Page 106: “Weighted mean of HRG codes FD11D, FD11E and FD11F”	“ HRG code WF01A ”	HRG codes reported in the CS (Table 43) for outpatient care visits were WF01A.	The EAG agrees. The table has been amended.									
Page 138: “Co-codamol, 2 (60/1000 mg) QDS”	“Co-codamol, 2 (30/500 mg) QDS”	Co-codamol dosage reported in CS (Table 44) in line with TA730/TA488, was 30/500 mg.	The EAG agrees. The table has been amended.									

Page 111: “Tornado diagram, ripretinib versus BSC, includes decision modifier of 1.7* ”	Add the corresponding text for (1.7*) to the Figure 31 legend or remove the asterisk	The asterisk marker in the title does not have a corresponding footnote in the legend.	The asterisk has been removed.
Page 102: “BSC costs, PD state (per 28-day cycle), Ripretinib; £0.00, BSC; £30.24 ”	“BSC costs, PD state (per 28-day cycle), Ripretinib; £30.24, BSC; £30.24 ”	BSC costs of £30.24 in the PD state apply to both ripretinib and BSC.	The table describes the original model. The table has been amended to include a cost of £0 for patients in the PDon state and £30.24 for patients in the PDOff state.
Page 104, table 34: “Ripretinib (on treatment) resource use; 0.0%, Estimated cost per 28-day cycle; £0.00”	The % PD patients (resource use) values should be amended so that Ripretinib (on treatment) are the same as Ripretinib (off treatment) for all drugs (column 3 should include the same values as column 4) Consequently, the expected cost per 28-day cycle for Ripretinib (on treatment) should match the PD ripretinib off-treatment/BSC costs (column 9 should include the same values as column 10; total cost for column 9 should be £30.24)	Pain management resource use and costs are the same for ‘ripretinib (on treatment)’ and ‘ripretinib (off treatment/BSC.’	The text reflects the original model. The final post-clarification version of the model is described in Chapter 5. No amendment is required.
P121: “... , a longer observation period (during which more patients initiated post-progression ripretinib) would effectively increase the sample size for	“... , a longer observation period (during which more patients initiated post-progression ripretinib) would, in theory , effectively increase the sample size for two-	Progression was not captured post the DCO 2021. As such, there would be more deaths, but not	Please refer to the earlier response relating to the 2022 DCO.

two-stage estimation. This, in turn, is expected to improve the statistical precision of the resulting analyses.”	stage estimation, if more progressions were collected. However, the 2022 DCO only captured survival data and not progression. ~~This, in turn, is expected to improve the statistical precision of the resulting analyses.”~~ (Reference: Deciphera, Clinical Study Protocol 20218)	progressions. Thus there would not be an increase in sample size in the stage 1 estimation of post-progression survival.	

Issue 8 Confidentiality marking

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
EAG report, page 17	Unpublished comments for 2024 advisory board	“The minutes of the company’s 2024 advisory board meeting suggest that clinical advisors considered that a model-predicted probability of OS of [REDACTED] at 10 years was an overestimate and a probability of [REDACTED] was more realistic.”	The confidentiality marking has been amended as requested
EAG report, page 17	Unpublished analysis from INVICTUS	“(predicted probabilities of 10-year OS = [REDACTED] and [REDACTED], respectively)”	The confidentiality marking has been amended as requested
EAG report, page 17	Unpublished analysis from INVICTUS	“The EAG’s preferred analysis uses the log-logistic model fitted to these adjusted data because it gives a predicted probability of 10-year OS for ripretinib of [REDACTED] which is close to the estimate of [REDACTED] provided by the clinical experts at the company’s advisory board meeting”	The confidentiality marking has been amended as requested

EAG report, page 109	Unpublished outputs from the cost-effectiveness model	Figure 29: Cost-effectiveness plane, ripretinib versus BSC, includes decision modifier of 1.7 (drawn by the EAG)	The confidentiality marking has been amended as requested
EAG report, page 126	Unpublished comments for 2024 advisory board	“Amongst the seven clinical advisors who attended the meeting, one advisor considered █ survival at 10-years to be plausible (as described above), one commented that █ OS at 10 years was an overestimate and following the meeting, four clinical advisors provided estimates of 10-year OS for ripretinib of █ and █, all of which are lower than the predicted OS from the log-logistic model selected by the company.”	The confidentiality marking has been amended as requested
EAG report, page 126	Unpublished outputs from the cost-effectiveness model	“...the company decided that a 10-year OS probability of █ was “too low” and the estimate of █ based on the log logistic model is plausible”	The confidentiality marking has been amended as requested
EAG report, page 128	Unpublished outputs from the cost-effectiveness model	“With respect to the ripretinib group, the clinical advisor considered that a predicted 10-year OS probability of █ was “ <i>too optimistic</i> ”, even in the situation in which ripretinib is used post-progression. The clinical advisor instead considered the Weibull and exponential models to be more clinically plausible; these models suggest 10-year OS	The confidentiality marking has been amended as requested

		probabilities of [REDACTED] and [REDACTED], respectively.”	
EAG report, page 140	Unpublished outputs from the cost-effectiveness model	Table 49: EAG preferred analysis results – ripretinib versus BSC, decision modifier = 1.7 <u>Please mark the QALYs, Costs, Inc. QALYs, and Inc. Costs in this table as confidential.</u>	The confidentiality marking has been amended as requested
EAG report, page 142-143	Unpublished outputs from the cost-effectiveness model	Table 50: EAG additional sensitivity analysis results – ripretinib versus BSC. [REDACTED] in this table as confidential.	The confidentiality marking has been amended as requested
EAG report, page 145	Unpublished outputs from the cost-effectiveness model	“...the company’s mean estimate of the QALYs for the BSC comparator group ([REDACTED] QALYs), the York Shortfall Calculator suggests an absolute shortfall of [REDACTED] QALYs and a proportional shortfall of [REDACTED]. This indicates that a decision modifier of 1.7 is appropriate. The EAG’s preferred analysis applies a generalised gamma distribution for OS in the BSC group resulting in less health gain in the comparator group ([REDACTED] QALYs), thereby also indicating that a decision modifier of 1.7 is appropriate”	The confidentiality marking has been amended as requested
EAG report, page 147	Unpublished outputs from the cost-effectiveness model	“These models are less optimistic than the company’s selected log-logistic distribution as they suggest predicted	The confidentiality marking has been amended as requested

		probabilities of OS at 10 years of approximately ■"	

Please note that the post-FACT version of the EAG report includes additional minor editorial and formatting changes. In addition, Figure 36 has been removed as this plot was already provided in Figure 35.