Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende avapritinib til behandling af inoperabel eller metastatisk gastrointestinal stromal tumor med D842V-mutation i PDGFRA

Vers. 1.0

Bilagsoversigt

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

April 26th 2024

Blueprint Medicines response to Medicinrådets Udkast anbefaling vedr. avapritinib til behandling af inoperabel eller metastatisk gastrointestinal stromal tumor med D842V mutation i PDGFRA

Blueprint Medicines would like to thank and acknowledge the substantial work Medicinrådet has done to assess the new drug Avapritinib for the treatment of adult patients with unresectable, metastatic GIST with PDGFRA D842V mutation in Denmark. We would like to clarify and address the following points made in the assessment report.

Point 1: Burden of disease and unmet medical need

Blueprint Medicines confirms Medicinrådet's summary in rare cases (1 patient approximately every 2 years in Denmark), patients have a specific mutation D842V in PDGFRA. The known drugs for the treatment of GIST have been described as ineffective on GIST with PDGFRA-D842V mutation. Therefore, patients with metastatic GIST with PDGFRA-D842V often survive significantly shorter (approx. 1-2 years) than patients with metastatic GIST overall (approx. 4-5 years). As this is a rare disease the budget impact with 1-2 patients per year in Denmark is relatively low and the unmet medical need is high.

Point 2: Treatment discontinuation needs to be factored into the extrapolation of long-term survival cost calculation

Medicinrådet notes on page 27/28 that the most significant change is the use of the survival data used for extrapolation of long-term survival in the economic model, where the Medicinrådet uses the observed survival data from NAVIGATOR without censoring for treatment discontinuation as the data basis for extrapolation of survival for avapritinib and unadjusted survival data from BLU-285-1002. With only one observed death, one would in practice assume that patients treated with avapritinib largely do not die, which is inconsistent with the clinical data.

Blueprint medicines acknowledge this variance and attribute it to the potential underestimation of survival outcomes in the NAVIGATOR study compared to clinical practice. We recognize that excluding patients who discontinued treatment may have limited the representation of OS outcomes, as evidenced by the small fraction of deaths recorded before treatment discontinuation.

By using the uncensored OS data breaks any connection between ToT and treatment effect from avapritinib, hindering the ability to reflect the gradual loss of treatment effect post-discontinuation, as suggested by clinical experts. Direct extrapolation of "full" OS data may not fully capture this effect due to a short follow-up period and incomplete ToT data. Furthermore, it is also assumed that better survival would be expected in clinical practice when avapritinib is used first line for the treatment of GIST harboring D842V mutation, rather than when used at a later line of treatment as in NAVIGATOR.

Point 3: IPTW distribution

Medicinrådet notes on page 22 in the distribution of weights for the adjusted indirect comparison between NAVIGATOR and BLU-285-1002, 4 patients were assigned higher weights compared to the rest of the population and thus have a greater influence of the analysis.

Generally, when performing an IPTW analysis, extreme weights are to be expected, and the usual measure to control for these extreme weights is through truncation at the 1st and 99th percentile. Given the context of our data with limited baseline characteristics (such as ECOG-PS and race) as well as an already small sample size, truncation was not done. A balance needed to be struck between reducing variance in the evidence or further biasing the evidence by reducing the sample size even more, and thus reducing the generalisability of the results.

In either instance, limitations would still exist within our evidence base, which is to be expected in such a rare disease area where there have been no effective treatments available. Thus, we ask Medicinrådet to keep this into consideration, as this was one of the reasons why the unweighted population was used in the base case of the assessment report, which had a significant impact in interpreting the long-term cost-effectiveness of avapritinib.

Point 4: ECOG status needs to be considered in the clinical trial

Medicinrådet notes on page 19/58 that without information about ECOG-PS, comparability between the populations (NAVIGATOR vs BLU-285-1002) cannot be fully assessed. Medicinrådet mentioned on page 35/58 that this is significant, as ECOG PS constitutes a prognostic factor, where higher PS is associated with a shorter survival. When this information is not available, Medicinrådet cannot assess whether the applicant's adjustments in the indirect comparison result in more or less comparable study populations.

Blueprint Medicines recognizes this limitation. The BLU-285-1002 dataset lacks a specific baseline for the initiation of the first TKI in patients with unresectable or metastatic PDGFRA D842 GIST. Instead, the dataset uses the initiation of the absolute first TKI for GIST, which may include treatments used in the adjuvant setting. To align with the NAVIGATOR dataset, the baseline was adjusted accordingly. However, this adjustment reduced the number of included patients and prevented the inclusion of ECOG performance status and race in the logistic model for propensity score estimation. Despite these limitations, the adjusted data closely resemble the baseline of the NAVIGATOR dataset, making the IPW-adjusted Kaplan–Meier data the most robust comparison available.

Conclusions

The avapritinib clinical development program remains the most comprehensive evidence base for unresectable or metastatic GIST with PDGFRA D842V mutation to date and remains the only approved treatment for this population with high unmet medical need. The evidence base will have limitations due to the nature of this ultra rare indication. As a company, we have provided the best available evidence. We hope Medicinrådet will consider all the above-mentioned points in its decision.

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25.04.2024
BMC/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	22.05.2024
Leverandør	Blueprint Medicines
Lægemiddel	Ayvakyt (avapritinib)
Ansøgt indikation	Monoterapi til behandling af voksne med inoperabel eller metastatisk gastrointestinal stromal tumor med D842V mutation i platelet derived growth factor alpha (PDGFRA)
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Ayvakyt (avapritinib):

Tabel 1: Forhandlingsresultat, betinget pristilbud

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Ayvakyt	100 mg	30 stk.	211.200	[redacted]	[redacted]
Ayvakyt	200 mg	30 stk.	211.200	[redacted]	[redacted]
Ayvakyt	300 mg	30 stk.	211.200	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling af Ayvakyt til behandling af **både** gastrointestinal stromal tumor (GIST) og til behandling af aggressiv systemisk mastocytose (ASM).

Hvis Medicinrådet ikke anbefaler Ayvakyt til begge indikationer, indkøbes lægemidlet til følgende forhandlede pris.

Tabel 2: Ubetinget pristilbud

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	SAIP, (DKK)	Rabatprocent ift. AIP
Ayvakyt	100 mg	30 stk.	211.200	[redacted]	[redacted]
Ayvakyt	200 mg	30 stk.	211.200	[redacted]	[redacted]
Ayvakyt	300 mg	30 stk.	211.200	[redacted]	[redacted]

Aftaleforhold

Amgros vil indgå en aftale med leverandøren, som gælder fra den 23.05.2024. Leverandøren har mulighed for at sætte prisen ned i hele aftaleperioden.

Konkurrencesituationen

Der er på nuværende tidspunkt ingen godkendt medicinsk behandling til voksne med inoperabel eller metastatisk gastrointestinal stromal tumor med D842V mutation i platelet derived growth factor alpha (PDGFRA).

Tabel 3 viser lægemiddeludgiften for et års behandling.

Tabel 3: Lægemiddeludgift pr. patient

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Ayvakyt (avapritinib)	300 mg	30 stk.	300 mg én gang dagligt	[redacted] Betinget pris	[redacted]
Ayvakyt (avapritinib)	300 mg*	30 stk.	300 mg én gang dagligt	[redacted] Ubetinget pris	[redacted]

Status fra andre lande

Tabel 4: Status fra andre lande

Land	Status	Kommentar	Link
Norge	Under vurdering	Bestillerforum har bestilt en vurdering i februar 2020. Firmaet har ikke sendt en ansøgning endnu.	Link til vurdering
Sverige	Ikke ansøgt		
England	Leverandøren har trukket ansøgningen tilbage		Link til status

Application for the assessment of avapritinib (Ayvakyt®) for the treatment of patients with unresectable or metastatic gastrointestinal stromal tumours harboring the platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation

Contact information

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Tables and Figures

Abbreviations

Abbreviation	Meaning
1L	First line. In the model, PF 1L is referring to AVA/IMA
2L	Second line. In the model, PF 2L is referring to SoC1
3L	Third line. In the model, PF 3L is referring to SoC2
AE	Adverse event
AIC	Akaike information criterion
AIP	Apotekernes indkøbspris (PPP – pharmacy purchasing price)

AVA	Avapritinib
BIC	Bayesian information criterion
BSC	Best supportive care
CBR	Clinical benefit rate
CEM	Cost-effectiveness model
CR	Complete Response
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
DC	Data cut
DCR	Disease control rate
DKK	Danish krone
DMC	Danish Medicines Council
DMCG	Danske Multidisciplinære Cancer Grupper
DOR	Duration of response
DRG	Diagnosis-related groups
ECM	Established clinical management
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30
EQ-5D	EuroQol-5-Dimension Questionnaire
EQ-5D-5L	EuroQol-5-Dimension 5-level Questionnaire
ESMO	European Society of Medical Oncology
GI	Gastrointestinal
GIST	Gastrointestinal stromal tumours
HCRU	Healthcare resource utilization
HADS	Hospital Anxiety and Depression Scale
HRQoL	Health-related quality of life
HSUV	Health state utility value
IC50	Maximal inhibitory concentration
ICER	Incremental cost-effectiveness ratio
IMA	Imatinib
ITC	Indirect treatment comparison
IPW	Inverse probability weighting
ITT	Intention-to-treat
KIT	v-Kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog
mRECIST	modified Response Evaluation Criteria in Solid Tumours
MRI	Magnetic resonance imaging
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence

ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PDGFRA	Platelet-derived growth factor receptor alpha
PF	Progression free
PFS	Progression free survival
PR	Partial Response
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
SD	Stable disease/Standard difference
SE	Standard error
SES	Self-Efficacy Scale
SF-36	Short-Form 36-item Health Survey
SmPC	Summary of product characteristics
SoC1	Standard of care. In the model, PF 2L is referring to SoC1
SoC2	Standard of care. In the model, PF 3L is referring to SoC2
TA	Technology appraisal
TKI(s)	Tyrosine kinase inhibitor(s)
ToT	Time on treatment
U/M	Unresectable or metastatic

1. Regulatory information on the pharmaceutical

Overview of the pharmaceutical	
Proprietary name	Ayvakyt®
Generic name	Avapritinib
Therapeutic indication as defined by EMA	Avapritinib is indicated as monotherapy for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) harbouring the PDGFRA D842V mutation (1).
Marketing authorization holder in Denmark	Blueprint Medicines (Netherlands) B.V.
ATC code	L01EX18
Combination therapy and/or co-medication	Given as monotherapy.
(Expected) Date of EC approval	EC approval was adopted for avapritinib on the 24th of September 2020 and granted avapritinib conditional market authorisation for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) harbouring the PDGFRA D842V mutation (1).
Has the pharmaceutical received a conditional marketing authorization?	Yes, avapritinib received conditional marketing authorisation for GIST on the 24th of September 2020. In order to further confirm the safety and efficacy of avapritinib in the treatment of adult patients with unresectable or metastatic GIST harbouring the PDGFRA D842V mutation, Blueprint Medicines (Netherlands) B.V. should submit the results of an observational safety and efficacy study in patients with unresectable or metastatic PDGFRA D842V mutant GIST. This is due December 2027 (1).
Accelerated assessment in the European Medicines Agency (EMA)	No.
Orphan drug designation (include date)	Granted orphan designation by the European Medicines Agency (EMA) for the treatment of GIST on the 17th of July 2017 (EU/3/17/1889) (2).
Other therapeutic indications approved by EMA	Avapritinib is indicated as monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN) or mast cell leukaemia (MCL), after at least one systemic therapy (1).
Other indications that have been evaluated by the DMC (yes/no)	**No.**
Dispensing group	**BEGR**
Packaging – types, sizes/number of units and concentrations	Ayvakyt® (avapritinib) 100 mg 30 x 100 mg film coated tablets Ayvakyt® (avapritinib) 200 mg 30 x 200 mg film coated tablets Ayvakyt® (avapritinib) 300 mg 30 x 300 mg film coated tablets

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	Avapritinib is indicated as monotherapy for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) harbouring the PDGFRA D842V mutation (1).
Dosage regiment and administration:	300 mg orally once daily on an empty stomach. Treatment should be continued until disease progression or unacceptable toxicity occurs (1).
Choice of comparator	Established clinical management (ECM). Although there is no approved treatment for this patient group, ECM consisting of TKIs included in the BLU-285-1002 and best supportive care (BSC) is considered to best reflect the clinical practice.
Prognosis with current treatment (comparator)	Unresectable or metastatic GIST harbouring the PDGFRA D842V mutation does lead to decreased life expectancy without treatment or current treatment. Median overall survival is 14.6 months (3).
Type of evidence for the clinical evaluation	Indirect comparison (inverse probability weighting).
Most important efficacy endpoints (Difference/gain compared to comparator)	ORR: 94.7% (avapritinib) OS KM Estimates at 24 months: Avapritinib = 76.9% vs TKI therapy = 38.0% (indirect comparison) PFS KM Estimates at 24 months: Avapritinib = 71.3% vs TKI therapy = 6.0% (indirect comparison)
Most important serious adverse events for the intervention and comparator	Avapritinib: Anaemia = 10.8% and disease progression = 8.0%
Impact on health-related quality of life	Clinical documentation: TA86/TA209: ECOG performance scores mapped to EQ-5D values by clinical experts as reported from the B222 trial. Result: 0.935 (CI: NA) TA179: EQ-5D questionnaire results collected from patients in the A6181004 trial. Result: 0.781 (CI: NA) VOYAGER trial: EQ-5D-5L questionnaire. Result: 0.782 (CI: NA) for SoC2 and 0.727 (CI: NA) for PD.
Type of economic analysis that is submitted	Cost-utility analysis Health state transition model
Data sources used to model the clinical effects	Avapritinib: IPW data censoring for discontinuation - from the NAVIGATOR study (data cut-off (DC): March 2020) ECM: IPW data from BLU-285-1002 (4, 5).
Data sources used to model the health-related quality of life	TA87/TA209, TA179, and VOYAGER trial (6).
Life years gained	Total life years gained for avapritinib (discounted): XXXXXXXX Total life years gained for comparator (discounted): XXXXXXXX
QALYs gained	Total QALYs gained for avapritinib (discounted): XXXXXXXX Total QALYs gained for comparator (discounted): XXXXXXXX
Incremental costs	XXXXXXXX
ICER (DKK/QALY)	XXXXXXXX
Uncertainty associated with the ICER estimate	Utility value for AVA/1L: ERG considered the HSUV for the first line (AVA and ECM) of 0.935 implausibly high and instead suggested to use general utility for the same age group as patients in SoC1 health state. This suggestion has been explored in sensitivity analysis.

Summary	
	Extrapolation method for OS: A simple extrapolation of the full OS is insufficient due to the short follow-up period and incomplete ToT data. Therefore, a more appropriate approach is needed, explicitly linking ToT to OS, and allowing for a gradual loss of treatment effect. However, the direct OS extrapolation with Exponential parametric distribution is explored in sensitivity analyses. This has a major impact on the ICER.
Number of eligible patients in Denmark	Incidence: 0.5 Prevalence: currently 1 prevalent patient
Budget impact (in year 5)	XXXXXXXX

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

3.1 The medical condition

3.1.1 Pathophysiology

Gastrointestinal stromal tumour (GIST) is a rare soft tissue sarcoma that arises from the interstitial cells of Cajal and occurs throughout the gastrointestinal (GI) tract (7, 8). GIST is most commonly diagnosed between the ages of 50 and 80 years, with a median age between 60 and 65, and represents approximately 0.1–3.0% of all GI malignancies (9). More than 85% of patients with GIST have an oncogenic v-Kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (KIT) mutation (~75% of cases) or a platelet-derived growth factor receptor alpha (PDGFRA) mutation (~10% of cases) that drives tumour growth (10).

Of the patients who progress to unresectable or metastatic GIST, approximately 5–6% are estimated to have a mutation in the PDGFRA activation loop (exon 18), particularly the PDGFRA D842V mutation (substitution of aspartic acid with valine at 842 position) (11, 12). This mutation results in patients being resistant to existing standard tyrosine kinase inhibitors (TKIs) and thus not responding to treatment with these therapies.

This population – patients with unresectable or metastatic GIST harbouring the PDGFRA D842V mutation – is the population for which Blueprint Medicines was granted conditional marketing authorization for avapritinib (AYVAKYT®) by the European Medicines Agency (EMA). Therefore, this population is the focus of this submission.

3.1.2 Clinical presentation of the disease

GISTs may be asymptomatic (approximately 18% of cases), especially in the case of smaller tumours of the intestinal tract (13, 14). These tumours are therefore usually found incidentally during investigations or procedures for other conditions. Small-bowel GISTs may remain silent for a long period before presenting with an acute event such as haemorrhage or rupture. Symptomatic colorectal GISTs may present with abdominal pain, obstruction, and lower GI bleeding; oesophageal and gastro-oesophageal junction GISTs with may also present with dysphagia. Lack of awareness of the presenting features may lead to delayed diagnosis of GIST in some patients.

3.1.3 Diagnosis

Lack of awareness of the presenting features of GIST may lead to delayed diagnosis in some patients. Nevertheless, many GISTs are identified clinically because of symptoms. Gastrointestinal examinations, including endoscopy, sometimes reveal asymptomatic GIST, especially in the stomach (15).

The European Society of Medical Oncology (ESMO) has published guidelines for the diagnosis, treatment, and follow-up of GIST. These state that when small esophagogastric or duodenal nodules <2 cm in size are detected, endoscopic biopsy may be difficult and laparoscopic/laparotomic excision may be the only way to make a definitive histological diagnosis. Many of these small nodules, if diagnosed as GISTs, will be either low risk or entities whose clinical significance remains unclear. Therefore, the standard approach to patients with esophagogastric or duodenal nodules <2 cm is endoscopic ultrasound assessment and then follow-up, reserving excision for patients whose tumour increases in size or becomes symptomatic. The standard approach to tumours ≥2 cm in size is biopsy/excision because they are associated with a higher risk of progression if confirmed as GIST (16).

Pathologically, the diagnosis of GIST relies on morphology and immunohistochemistry. Mutational analysis for known mutations involving KIT and PDGFRA can confirm the diagnosis of GIST. Mutational analysis has a predictive value for sensitivity to molecular-targeted therapy and prognostic value. Its inclusion in the diagnostic work-up of all GISTs should be considered standard practice (16).

3.1.4 Patient prognosis

As a result of resistance to existing TKIs, patients with unresectable or metastatic GIST harbouring the PDGFRA D842V mutation have a poor prognosis, providing an expected overall response rate (ORR) of 0%, median progression-free survival (PFS) of only 3-5 months, and a median overall survival (OS) of 13-15 months (3, 5, 17).

A study by Osuch and colleagues reported that this group of patients had the worst expected survival outcomes out of all patients with GIST. This was compared with the overall advanced-GIST population, where patients had a median OS of 82 months (as high as 88 months for patients with exon 11 and exon 9 KIT mutations) and the probability of survival at 5 years was 75% (18). Therefore, there is a clear unmet need for an effective treatment option to improve the prognosis for patients with unresectable or metastatic GIST harbouring the PDGFRA D842V mutation.

3.1.5 The influence of the condition on the patients' functioning and health-related quality of life

Once patients become symptomatic, as is likely to be the case for patients with unresectable or metastatic disease, they are likely to face a significant burden from their symptoms. The most common symptoms of GIST include upper GI bleeding and anaemia, while larger tumours may present with abdominal pain/discomfort and a palpable mass. Some patients may also have other non-specific systemic symptoms such as nausea, vomiting, early satiety, weight loss, night sweats and fever (13), all of which will negatively impact their quality of life. Patients with metastatic disease will also experience additional symptoms depending on the site of their metastases.

GIST patients have been demonstrated to show significantly higher levels of fatigue and severe fatigue (compared to matched, healthy controls), with roughly one third of patients being classified as severely fatigued (19). Fatigue is defined as persisting and distressing physical, emotional and cognitive exhaustion that is unrelated to recent activity and interferes with the person's function (20). It has a negative impact on health-related quality of life (HRQoL) and can even lead to

disability (21). Severely fatigued GIST patients report significantly worse functional, psychological and physical well-being, as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30), the Hospital Anxiety and Depression Scale (HADS), and the Short-Form 36-item Health Survey (SF-36), respectively (19). These patients also reported significantly worse levels of independence, as captured by the Self-Efficacy Scale (SES) (19). Fatigue has also been associated with a number of psychological conditions, such as depression, anxiety, stress and catastrophizing (19, 22-26).

The HRQoL of patients with unresectable or metastatic GIST decreases rapidly as patients progress through the lines of therapy, particularly once they have exhausted all treatment options. In the National Institute for Health and Care Excellence (NICE) technology appraisal (TA) of imatinib, it was accepted that patients with unresectable or metastatic GIST receiving imatinib at first line have a utility value of 0.935 (27); at second line, patients receiving sunitinib have a utility value of 0.781 (28); at third line, patients receiving regorafenib have a utility value of 0.767 (29); and patients with progressive disease (PD) who have exhausted all treatment options have a utility value of 0.647 (29). A review conducted among clinicians in the UK reported an agreement on these values being reflective of the HRQoL of patients with unresectable or metastatic GIST with the PDGFRA D842V mutation in UK clinical practice (30). It would be expected that a large proportion of patients with the PDGFRA D842V mutation would have the lower utility values in clinical practice, as these patients are not likely to respond to established clinical management (ECM) with current TKIs and will therefore progress quickly through each line of treatment.

Patients with GIST also report experiencing high levels of fear relating to cancer recurrence or progression (31), likely due to the recurrent nature of the disease. In patients with unresectable or metastatic GIST with the PDGFRA D842V mutation, this is likely to be further compounded by the lack of effective treatment options and, consequently, faster disease progression and limited expected survival—resulting in even higher levels of fear and distress for these patients.

3.1.5.1 Impact on caregivers

Given the high median age at diagnosis and the potential for reduced levels of physical functioning and independence of GIST patients, it is expected there will also be an associated impact on caregivers. Some caregivers for these patients have been shown to experience a substantial burden, with significantly reduced mental health, less vitality, lower general health, high levels of distress, and significantly lower social functioning (32). Caregivers with high levels of distress also experienced more limitations in work and activities of daily living due to physical and emotional problems (32). For caregivers of patients with PDGFRA D842V-mutated GIST, these issues are likely to be compounded by the lack of available effective therapies and the progressive nature of the disease. Although data formally exploring this for patients with GIST are not available to our knowledge, this has been shown in other similar indications. For caregivers of patients with amyotrophic lateral sclerosis, it has been demonstrated that “the emotional impact of the diagnosis is severe, because of the steadily progressing fatal character of the disease and the lack of effective therapy”(33). Given that these concerns are similar to those for patients with PDGFRA D842V-mutated GIST, it is reasonable to assume that the effects on caregivers will be comparable.

Overall, patients with GIST experience a substantial burden from their disease, which has a significant negative impact on their HRQoL. This has been demonstrated to be worse for patients with unresectable or metastatic disease, who will likely face a higher symptom burden, and worse still for patients with the PDGFRA D842V mutation, who will be facing an additional psychological burden associated with the lack of effective treatment options. As patients with unresectable or metastatic PDGFRA D842V-mutated GIST are likely to become more caregiver dependent, due to the faster progression of their disease, their caregivers are also more anticipated to face additional burden and distress, with a significant impact on their own HRQoL.

3.2 Patient population

The incidence of GIST in Denmark is estimated to be 1-1.5/100 000 people, which corresponds to approximately 60 cases of new cases per year in Denmark (34, 35). Due to the very specific mutational status of the PDGFRA D842V mutation, limited information is available on the number of patients with this specific mutation in Denmark.

To best inform on potential patient numbers in Denmark, 2 Dutch publications on the national GIST registry may provide insights into the Danish healthcare system (36, 37). Based on the publications, of all the GIST patients, 6.2% have the PDGFRA exon 18 mutation, of which, 72.7% harbour the D842V mutation. From these patients, 10% are considered operable/metastatic, a key prognostic factor for avapritinib. With this information, for an incidence of 60 GIST patients per year in Denmark, this results in approximately 0.3 cases per year, or one patient with unresectable or metastatic GIST harbouring the PDGFRA D842V mutation every 2 years.

This has formed the basis on the market forecasting done in Denmark. Of the Danish patients who have progressed to unresectable or metastatic GIST harbouring the PDGFRA D842V mutation, Blueprint Medicines estimates 1 patient every second year is seen by the Danish healthcare system and therefore would be eligible for treatment with avapritinib (38). Regarding the prevalence of unresectable or metastatic GIST harbouring the PDGFRA D842V mutation, according to the applicant's market research, 1 patient already diagnosed in 2021 is currently treated in Danish hospitals.

It is assumed that the recommendation of avapritinib in the Danish healthcare system will subsequently increase the number of eligible patients in Denmark in the coming years, since a treatment option would be available for unresectable or metastatic GIST patients harbouring the PDGFRA D842V mutation.

Table 1 Incidence and prevalence in the past 5 years

Year	2019	2020	2021	2022	2023
Incidence in Denmark	1	0	1	0	1
Prevalence in Denmark	1	1	1	1	1

Source: Blueprint Medicine Market research and communication [Data on file] (38)

The focus of this submission to the DMC is patients with unresectable or metastatic GIST harbouring the PDGFRA D842V. Estimated patient numbers over the next five years in Denmark is provided below. The number of eligible patients is expected to increase due to the increase of life expectancy associated with the use of avapritinib in GIST patients.

Table 2 Estimated number of unresectable or metastatic GIST patients harbouring the PDGFRA D842V mutation eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	1	1	2	2	2

Source: Blueprint Medicine Market research and communication [Data on file] (38)

3.3 Current treatment options

The Danish Medicines Council (DMC) has not currently developed treatment guidelines for patients with unresectable or metastatic GIST harbouring the PDGFRA D842V mutation in Denmark.

To best inform the relevant pharmaceutical comparators for this submission, the latest treatment guideline developed in 2020 by the Danske Multidisciplinære Cancer Grupper (DMCG) is most relevant in Denmark (34). The treatment recommendations from the DMCG align with international GIST guidelines such as the British Sarcoma Group (39), ESMO (16), and the National Comprehensive Cancer Network (NCCN) (40).

The gold standard treatment for GIST is surgical resection, preferably through laparoscopy, or with open laparotomy, if the patient is unstable (41). In patients with GIST without metastatic disease and for whom resection is possible, resection is performed with curative intent (42). Adjuvant therapy with imatinib for 3 years is the standard treatment of patients with a significant risk of relapse and a sensitive mutation (34, 39).

As chemotherapy and radiation are ineffective, the current treatment regimen in Denmark for metastatic or unresectable GIST involves sequential administration of the TKIs: imatinib (first line), sunitinib (second line), and regorafenib (third line) (16, 34, 43). These agents are indicated and approved for use in all patients with advanced GIST, regardless of mutational status. For patients with the PDGFRA D842V mutation, current TKI therapies have little benefit; once these patients progress to unresectable or metastatic disease, they have a significantly worse prognosis (30). Patients will also be managed with supportive measures to treat symptoms such as pain and bleeding, and surgery may also be considered for debulking of tumours. These options would be included alongside current TKI therapy, if chosen by the patients, or as part of best supportive care.

In Denmark, the DMCG guideline emphasises the importance of mutational testing of PDGFRA status for all GIST patients at the start of treatment, or at least shortly after initiating treatment (34). Until the results of the mutational status are obtained, all patients will start treatment with imatinib 400 mg (34).

Currently, there are no specific treatment recommendations for PDGFRA D842V mutated GIST patients in Denmark, the DMCG guidelines state current TKI therapies have little efficacy within this mutated patient group and note the lack of treatment options available for these patients in Denmark (34).

3.4 The intervention

Table 3 Key descriptive information of avapritinib

Overview of intervention	
Therapeutic indication relevant for the assessment	Avapritinib is indicated as monotherapy for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) harbouring the PDGFRA D842V mutation (1).
Method of administration	Oral tablets.
Dosing	300 mg orally once daily on an empty stomach (1).
Dosing in the health economic model (including relative dose intensity)	300 mg, dose intensity: 0.87
Should the pharmaceutical be administered with other medicines?	No, given as monotherapy.

Overview of intervention	
Treatment duration / criteria for end of treatment	Treatment should be continued until disease progression or unacceptable toxicity occurs (1).
Necessary monitoring, both during administration and during the treatment period	Haemorrhages (1) Avapritinib has been associated with an increased incidence of haemorrhagic adverse reactions, including serious and severe adverse reactions, like gastrointestinal haemorrhage and intracranial haemorrhage in patients with unresectable or metastatic GIST and AdvSM. Gastrointestinal haemorrhagic adverse reactions were the most commonly reported haemorrhagic adverse reactions during avapritinib treatment of unresectable or metastatic GIST patients, while hepatic and tumour haemorrhage also occurred. Routine surveillance of haemorrhagic adverse reactions must include physical examination. Complete blood counts, including platelets, and coagulation parameters must be monitored, particularly in patients with conditions predisposing to bleeding, and in those treated with anticoagulants (e.g. warfarin and phenprocoumon) or other concomitant medicinal products that increase the risk of bleeding. Intracranial haemorrhages Adverse reactions of intracranial haemorrhage occurred in patients who received avapritinib. Before initiating avapritinib the risk for intracranial haemorrhage should be carefully considered in patients with potential increased risk including those with thrombocytopenia, vascular aneurysm or a history of intracranial haemorrhage or cerebrovascular accident within the prior year. Patients who experience clinically relevant neurological signs and symptoms (e.g. severe headache, vision problems, somnolence, and/or focal weakness) during treatment with avapritinib must interrupt dosing of avapritinib and inform their healthcare professional immediately. Brain imaging by magnetic resonance imaging (MRI) or computed tomography (CT) may be performed at the discretion of the physician based on severity and the clinical presentation. For patients with observed intracranial haemorrhage during treatment with avapritinib, regardless of severity grade, avapritinib must be permanently discontinued. Unresectable or metastatic GIST Serious adverse reactions of intracranial haemorrhage were reported in patients with unresectable or metastatic GIST receiving avapritinib. The exact mechanism is unknown. There is no clinical study experience using avapritinib in patients with brain metastases. Cognitive effects Cognitive effects, such as memory impairment, cognitive disorder, confusional state, and encephalopathy, can occur in patients receiving avapritinib. The mechanism of the cognitive effects is not known. It is recommended that patients are clinically monitored for signs and symptoms of cognitive events such as new or increased forgetfulness, confusion, and/or difficulty with cognitive functioning. Patients must notify their healthcare professional immediately if they experience new or worsening cognitive symptoms. In clinical studies, dose reductions or interruptions improved Grade ≥2 cognitive effects compared to no action. Fluid retention

Occurrences of fluid retention, including severe cases of localised oedema (facial, periorbital, peripheral oedema and/or pleural effusion) or generalised oedemas, have been reported with a frequency category of at least common in patients with unresectable or metastatic GIST taking avapritinib. Other localised oedemas (laryngeal oedema and/or pericardial effusion) have been reported uncommonly. Therefore, it is recommended that patients be evaluated for these adverse reactions including regular assessment of weight and respiratory symptoms. An unexpected rapid weight gain or respiratory symptoms indicating fluid retention must be carefully investigated and appropriate supportive care and therapeutic measures, such as diuretics, should be undertaken. For patients presenting with ascites, it is recommended to evaluate the aetiology of ascites.

QT interval prolongation

Prolongation of QT interval has been observed in patients with unresectable or metastatic GIST and AdvSM treated with avapritinib in clinical studies. QT interval prolongation may induce an increased risk of ventricular arrhythmias, including Torsade de pointes. Avapritinib should be used with caution in patients with known QT interval prolongation or at risk of QT interval prolongation (e.g. due to concomitant medicinal products, pre-existing cardiac disease and/or electrolyte disturbances). Concomitant administration with strong or moderate CYP3A4 inhibitors should be avoided due to the increased risk of adverse reactions, including QT prolongation and related arrhythmias. Interval assessments of QT by electrocardiogram (ECG) should be considered if avapritinib is taken concurrently with medicinal products that can prolong QT interval.

Gastrointestinal disorders

Diarrhoea, nausea and vomiting were the most commonly reported gastrointestinal adverse reactions in patients with unresectable or metastatic GIST. Patients who present with diarrhoea, nausea and vomiting should be evaluated to exclude disease-related aetiologies. Supportive care for gastrointestinal adverse reactions requiring treatment may include medicinal products with antiemetic, antidiarrheal, or antacid properties. The hydration status of patients experiencing gastrointestinal adverse reactions must be closely monitored and treated as per standard clinical practice

Laboratory tests

Treatment with avapritinib in patients with unresectable or metastatic GIST is associated with anaemia, neutropenia and/or thrombocytopenia. Complete blood counts must be performed on a regular basis during the treatment with avapritinib. Treatment with avapritinib is associated in patients with unresectable or metastatic GIST with elevations in bilirubin and liver transaminases. Liver function (transaminases and bilirubin) should be monitored regularly in patients receiving avapritinib

CYP3A4 inhibitors and inducers

Co-administration with strong or moderate CYP3A inhibitors should be avoided because it may increase the plasma concentration of avapritinib. Co-administration with strong or moderate CYP3A inducers should be avoided because it may decrease the plasma concentrations of avapritinib.

Overview of intervention	
	Photosensitivity reaction Exposure to direct sunlight must be avoided or minimised due to the risk of phototoxicity associated with avapritinib. Patients must be instructed to use measures such as protective clothing and sunscreen with high sun protection factor (SPF).
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	GIST patients must receive mutational testing for the PDGFRA D842V mutation before initiating treatment with avapritinib (34).
Package size(s)	Ayvakyt® (avapritinib) 100 mg, 200 mg and 300 mg available as 30 film coated tablets

3.4.1 Treatment with avapritinib

Blueprint Medicines has developed avapritinib (AYVAKYT®) as the first precision medicine that specifically targets the PDGFRA D842V mutation. It has demonstrated unprecedented efficacy in the subgroup of patients with unresectable or metastatic GIST harbouring this mutation—patients that currently have no effective treatment options available. The availability of avapritinib thus represents a clear step change in the management of unresectable or metastatic GIST for these patients.

3.4.1.1 Mechanism of action

Avapritinib is a Type 1 TKI that binds to the active conformation and inhibits a broad range of PDGFRA - and KIT-mutant kinases at clinically relevant concentrations (44). Constitutive activation of PDGFRA and KIT receptor tyrosine kinases have been implicated in the pathogenesis of a number of malignancies and rare haematological diseases. In in vitro biochemical assays, avapritinib inhibited the activity of PDGFRA exon 18 mutants (D842V, D842I, and D842Y). Avapritinib has demonstrated biochemical in vitro activity on the PDGFRA D842V (44) that are associated with resistance to imatinib, sunitinib, and regorafenib—with maximal inhibitory concentration (IC50) values of 0.24 nM.

3.4.2 The intervention in relation to Danish clinical practice

Given that mutational testing of PDGFRA status is already part of routine clinical practice in Denmark and no other effective treatments are available (34), avapritinib would become the only effective treatment option available to Danish patients with unresectable or metastatic GIST harbouring the PDGFRA D842V-mutation. It is expected that all eligible patients would receive it following a positive recommendation as first line treatment. This is in line with recommendations made by both local Danish (34) and international guidelines (16, 39, 40), which recommend avapritinib as the first line of therapy for GIST patients once the PDGFRA D842V mutational status has been confirmed.

3.5 Choice of comparator(s)

Due to the very specific mutational status, there are currently no effective treatments approved in Denmark for GIST patients harbouring the PDGFRA D842V mutation. However, in clinical practice, it is still expected some clinicians may attempt treating patients standard TKI therapy, such as imatinib, sunitinib and regorafenib, followed by best supportive care. This is also reflective of

Swedish clinical practice, where a proportion of GIST patients harbouring the PDGFRA D842V mutation may still receive TKI based therapy and in particular imatinib (45).

For the purposes of this submission, a comparison versus placebo was not feasible due to the lack of data and to ethical concerns. Therefore, the appropriate choice of comparators for GIST patients harbouring the PDGFRA D842V mutation that best reflect current clinical treatment in Denmark would be TKI therapy, specifically imatinib, sunitinib and regorafenib (34). Details of the comparators are described in the tables below.

Table 4 Key descriptive information of imatinib

Overview of comparator	
Generic name	Imatinib
ATC code	L01EA01 (46)
Mechanism of action	Imatinib is a small molecule protein-tyrosine kinase inhibitor that potently inhibits the activity of the Bcr-Abl tyrosine kinase (TK), as well as several receptor TKs: Kit, the receptor for stem cell factor (SCF) coded for by the c-Kit proto-oncogene, the discoidin domain receptors (DDR1 and DDR2), the colony stimulating factor receptor (CSF-1R) and the platelet-derived growth factor receptors alpha and beta (PDGFR-alpha and PDGFR-beta). Imatinib can also inhibit cellular events mediated by activation of these receptor kinases (47)
Method of administration	Oral tablets.
Dosing	The recommended dose of imatinib is 400 mg per day for adult patients with unresectable and/or metastatic malignant GIST (47).
Dosing in the health economic model (including relative dose intensity)	Imatinib: 400 mg. Dose intensity: 1.00
Should the pharmaceutical be administered with other medicines?	No, given as monotherapy.
Treatment duration/ criteria for end of treatment	In clinical trials in GIST patients, treatment with imatinib was continued until disease progression. At the time of analysis, the treatment duration was a median of 7 months (7 days to 13 months). The effect of stopping treatment after achieving a response has not been investigated (47).
Need for diagnostics or other tests (i.e. companion diagnostics)	No.
Package size(s)	60 x 100 mg film coated tablets; 30 x 400 mg film coated tablets; 30 x 600 mg film coated tablets (46)

Table 5 Key descriptive information of sunitinib

Overview of comparator	
Generic name	Sunitinib
ATC code	L01EX01 (46)

Overview of comparator	
Mechanism of action	Sunitinib inhibits multiple RTKs that are implicated in tumour growth, neoangiogenesis, and metastatic progression of cancer. Sunitinib was identified as an inhibitor of platelet-derived growth factor receptors (PDGFRα and PDGFRβ), VEGF receptors (VEGFR1, VEGFR2, and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET). The primary metabolite exhibits similar potency compared to sunitinib in biochemical and cellular assays (48).
Method of administration	Oral tablets.
Dosing	50 mg taken orally once daily, for 4 consecutive weeks, followed by a 2-week rest period to comprise a complete cycle of 6 weeks (48).
Dosing in the health economic model (including relative dose intensity)	Sunitinib: 50 mg. Dose intensity: 0.97
Should the pharmaceutical be administered with other medicines?	No, given as monotherapy.
Treatment duration/ criteria for end of treatment	Treatment should be continued until disease progression or unacceptable toxicity occurs.
Need for diagnostics or other tests (i.e. companion diagnostics)	No.
Package size(s)	28 x 12.5 mg hard capsules; 28 x 25 mg hard capsules; 28 x 50 mg hard capsules; 30 x 12.5 mg hard capsules; 30 x 25 mg hard capsules; 30 x 50 mg hard capsules (46)

Table 6 Key descriptive information of regorafenib

Overview of comparator	
Generic name	Regorafenib
ATC code	L01EX05 (46)
Mechanism of action	Regorafenib is an oral tumour deactivation agent that potently blocks multiple protein kinases, including kinases involved in tumour angiogenesis (VEGFR1, -2, -3, TIE2), oncogenesis (KIT, RET, RAF-1, BRAF, BRAFV600E), metastasis (VEGFR3, PDGFR, FGFR) and tumour immunity (CSF1R). In particular, regorafenib inhibits mutated KIT, a major oncogenic driver in gastrointestinal stromal tumours, and thereby blocks tumour cell proliferation. In preclinical studies regorafenib has demonstrated potent antitumour activity in a broad spectrum of tumour models including colorectal, gastrointestinal stromal and hepatocellular tumour models which is likely mediated by its anti-angiogenic and anti-proliferative effects. In addition, regorafenib reduced the levels of tumour associated macrophages and has shown anti-metastatic effects in vivo. Major human metabolites (M-2 and M-5) exhibited similar efficacies, compared to regorafenib in in vitro and in vivo models (49).
Method of administration	Oral tablets.

Overview of comparator	
Dosing	160 mg taken once daily for 3 weeks followed by 1 week off therapy. This 4-week period is considered a treatment cycle (49).
Dosing in the health economic model (including relative dose intensity)	Regorafenib: 40 mg. Dose intensity: 0.87
Should the pharmaceutical be administered with other medicines?	No, given as monotherapy.
Treatment duration/ criteria for end of treatment	Treatment should be continued until disease progression or unacceptable toxicity occurs.
Need for diagnostics or other tests (i.e. companion diagnostics)	No.
Package size(s)	84 x 40 mg film coated tablets (46)

3.6 Cost-effectiveness of the comparator(s)

Imatinib, sunitinib and regorafenib have not been previously assessed by the DMC for GIST patients in general. According to the DMC methods guideline, if a comparator has not previously been assessed by the DMC, a comparison against placebo should be made, including cost-effectiveness (50). The comparison of avapritinib against placebo in an orphan setting such as this is simply not possible as there is no published clinical evidence of placebo's efficacy in GIST patients harbouring the PDGFRA D842V mutation. To date, the avapritinib clinical development program remains the best clinical evidence available for this patient population.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Table 7 Efficacy outcome measures relevant for the application

Outcome measure	Time point	Definition	How was the measure investigated/method of data collection
Overall response rate (ORR)	March 2020 DC	The primary efficacy endpoint of ORR was defined as the proportion of patients with a confirmed best response of CR or PR, where CR or PR had to be confirmed at a subsequent assessment without intervening progression. The primary analysis of ORR was conducted by central radiology per mRECIST Version 1.1. ORR was estimated using frequency, percentage, and two-sided 95% CIs based on the exact binomial distribution (Clopper–Pearson) for the safety population. Additionally, the best overall response following the hierarchical order of CR, PR, SD, PD and NE was tabulated for the prespecified subpopulations in the safety population.	Central radiology per mRECIST Version 1.1

Outcome measure	Time point	Definition	How was the measure investigated/method of data collection
		Logistic regression was fitted to assess the effect of factors individually on the ORR, including starting dose, maximum daily dose level, dose intensity, age, ECOG status, size of largest tumour mass, etc., stratified by mutation type. Factors that were significant at the 0.2 level in univariable models were entered in the final multivariable model.	
Complete response (CR)	March 2020 DC		Central radiology per mRECIST Version 1.1
Partial response (PR)	March 2020 DC		Central radiology per mRECIST Version 1.1
Stable disease (SD)	March 2020 DC		Central radiology per mRECIST Version 1.1
Progressive disease (PD)	March 2020 DC		Central radiology per mRECIST Version 1.1
Clinical benefit rate (CBR)	March 2020 DC	Defined as the proportion of patients with a confirmed CR/PR, or SD lasting for four cycles (16 weeks). The response was assessed per mRECIST Version 1.1 by central radiology and investigator. CBR was estimated using frequency, percentage, and two-sided 95% CIs based on the exact binomial distribution.	Central radiology per mRECIST Version 1.1
Disease control rate (DCR)	March 2020 DC	Defined as the proportion of patients with a confirmed CR,PR, or SD	Central radiology per mRECIST Version 1.1
Duration of response (DOR)	March 2020 DC	Defined as the time from first documented response (CR/PR) to the date of first documented disease progression or death due to any cause, whichever occurred first. The date of disease progression was based on central radiology assessment per mRECIST Version 1.1. Patients without confirmed CR or PR were excluded from this analysis. Patients who were still responding to treatment at the time of data cut-off were censored at their last valid assessment. The analysis was primarily based on the FDA Guidance for Cancer Trial Endpoints. The censoring rules based on the EMA guidelines were used as a sensitivity analysis. DoR was analysed using KM methods and included the estimated median with two-sided 95% CI and 25th and 75th percentiles. DoR at specific timepoints (e.g. 3-, 6- and 12-month, etc.) was computed, along with the standard errors using Greenwood's formula. Sensitivity analysis was conducted for DoR based on investigator assessment per mRECIST Version 1.1, or central radiology assessment per Choi criteria for the safety population. Both FDA and EMA censoring rules were applied.	Central radiology per mRECIST Version 1.1
Time to response	March 2020 DC	Defined as the time from the start of treatment to the time the response criteria for CR or PR were first met per mRECIST Version 1.1. Patients without a confirmed CR or PR were excluded from this analysis. If all scans were not done on the same date, the response date was the date of the first assessment.	Central radiology per mRECIST Version 1.1

Outcome measure	Time point	Definition	How was the measure investigated/method of data collection
		Summary statistics were presented by starting doses, and the time to response was compared between starting doses using the Wilcoxon rank sum test, with patients with the longest time to response having the highest rank. Plot of cumulative probability of response was provided by starting dose.	
Overall survival (OS)	January 2021 DC	Defined as the time from the start of treatment to the date of death. Patients who died before or on the data cut-off date were considered to have had an OS event. Patients who did not have death recorded prior to or on the cut-off date were censored at the last date known alive. Last date known alive was defined as the last non-imputed date of any patient record prior to or on the data cut-off date in the clinical database. It could be the last visit date or last contact date that the patient was known to be alive. The survival distribution of OS was estimated using the KM method. The median OS, along with its two-sided 95% CI and 25th and 75th percentiles, were estimated. In addition, the survival rate at specific timepoints (e.g., 3-, 6- and 12-month, etc.) were computed, along with the standard errors using Greenwood's formula. The plots of survival curves using the KM method were presented. Unstratified Cox proportional hazards model of OS was fitted as a sensitivity analysis	Central radiology per mRECIST Version 1.1
Progression-free survival (PFS)	March 2020 DC	Defined as the time from the start of treatment to the date of first documented disease progression or death due to any cause, whichever occurred first. The date of disease progression was based on central radiology assessment per mRECIST Version 1.1. Specifically, if not all scans were done on the same date, the first scan date was used. If a patient had not had an event, PFS was censored at the date of last valid assessment that was stable or better. The KM method was used to estimate the survival distribution function. The median PFS along with its two-sided 95% CI and 25th and 75th percentiles were estimated. In addition, the event rates (or event-free rates) at specific timepoints (e.g. 3-, 6- and 12-month, etc.) were computed, along with the standard errors using Greenwood's formula. Survival curves using the KM method were presented. A Cox proportional hazards model was used to estimate hazard ratios of factors such as starting daily dose, maximum daily dose level, dose intensity, age, ECOG status, size of largest tumour mass, etc., along with 95% CIs. The model was stratified by mutation type (exon 18 versus not). Factors that are significant at the 0.2 level in univariable models were entered into the final multivariable model. Unstratified analysis based on the safety population was conducted.	Central radiology per mRECIST Version 1.1
Radiographic tumour reductions	March 2020 DC		Central radiology per mRECIST Version 1.1

Source: NAVIGATOR CSR (51)

Validity of outcomes

Disease response to treatment was assessed using radiographic and clinical assessments. These tests and evaluations are standard and appropriate for the evaluation of patients with GIST and were based on appropriate response criteria that are widely accepted as valid and reliable measures of response to treatment. Selection of the primary endpoint of ORR was based on the FDA's May 2007 Guidance for Industry on Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics for single-arm studies (51).

OS and PFS are standard efficacy outcomes often used in oncology studies and has been used in previous DMC submissions.

4. Health economic analysis

A cost-utility analysis was conducted based on a Danish adaptation of an Excel-based cost-effectiveness model (CEM). The objective of the CEM is to assess the cost-effectiveness of avapritinib versus established clinical management (ECM) in unresectable/metastatic PDGFRA D842V-mutated GIST. In the following sections the model is described in section 8.1, the outcomes and inputs in the model are summarized in sections 8.2.1, and section 8.6 presents the results. The model outcomes include total and incremental costs and health outcomes expressed as quality-adjusted life years (QALYs) gained.

4.1 Model structure

A health state transition model is used to perform the cost-utility analysis and estimate long-term costs and health benefits of avapritinib. This model structure with five discrete health states follows patients through the existing and prospective (avapritinib) treatment pathways. The probability of being in each of these health states is driven by parametric extrapolation of progression-free survival (PFS), overall survival (OS), and time on treatment (ToT) data from the NAVIGATOR and the BLU-285-1002 and was confirmed by clinical experts (52). The model structure focuses on the ability of avapritinib to inhibit disease progression, which in turn is associated with an OS benefit. The patient flow through the model structure is visualised in Figure 1.

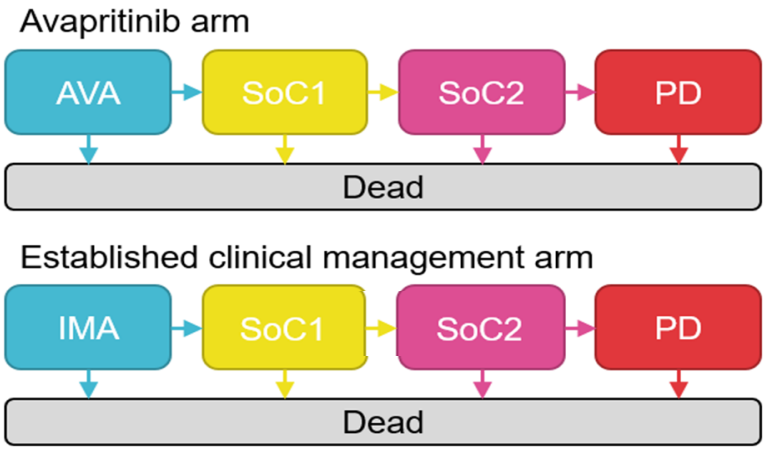

Figure 1 Model structure

Abbreviations: AVA: avapritinib; SoC: standard of care, PD: progressed disease, IMA: imatinib

Figure 1 shows that patients in the avapritinib arm are treated at baseline with avapritinib, and patients in the ECM arm may be treated with first line imatinib. According to clinical experts, D842V GIST patients failing first-line treatment would receive best supportive care (BSC) and not be subsequently treated with other non-targeted TKIs (45). Despite receiving treatment, some patients continue to experience disease progression. Therefore, a comprehensive cost-

effectiveness model should include additional stages of disease beyond the initial progression. Two standard-of-care (SoC) states, namely SoC1 and SoC2, represent these stages.

In both treatment arms (avapritinib and ECM), patients in the SoC1 and SoC2 health states are allocated the same costs for healthcare resource utilization (HCRU) and utilities. The probability of transition from SoC1 to SoC2 and from SoC2 to progressive disease (PD) are the same in both arms, obtained by extrapolation of the IPW-adjusted PFS for second- and third-line treatments in the BLU-285-1002 trial (base case).

However, as mentioned in section 3.5, a low overall response rate to imatinib first line, to second-line sunitinib and third-line regorafenib are seen among patients with unresectable/metastatic PDGFRA D842V-mutated GIST, and based on statements from Nordic clinical experts, these patients are unlikely eligible for treatment with non-targeted TKIs in Danish settings (38) (52). To reflect the uncertainty surrounding current clinical practice for the treatment of unresectable/metastatic PDGFRA D842V-mutated GIST patients, the base case assumes that only 20% of patients incur costs of imatinib and that no patients incur costs of second line sunitinib and third line regorafenib. To further address this uncertainty, a scenario analysis assumes that the proportion of patients incurring the costs of TKIs in ECM arm is set to 0% for all three lines. Finally, another scenario analysis will align efficacy and costs and assume that all patients incur efficacy from the BLU-285-1002 study and costs from receiving imatinib, sunitinib and regorafenib.

Patients in both the intervention and the comparator arm who survive and encounter disease progression upon reaching the SoC2 state move into the progressive disease health state. This state is linked to a lower health state utility value and higher HCRU compared to all prior states. This is done to reflect the deterioration of the disease as patients progress through the treatment regimen.

4.2 Model features

Table 8 describes the model features.

Table 8 Features of the economic model

Model features	Description	Justification
Patient population	Adult patients with PDGFRA D842V-mutated GIST	Patient population according EMA label.
Perspective	Limited societal perspective	According to DMC guidelines (53).
Time horizon	Lifetime (40 years)	To capture all health benefits and costs in line with DMC guidelines (53). Based on mean age of patients in the NAVIGATOR trial (61.70) and the mean age of diagnosis in the Danish population (65 years) (54) (55).
Cycle length	1 month	Consistent with length of treatment cycle.
Half-cycle correction	Yes	To adjust for the distribution of costs and benefits accrued throughout each cycle.
Discount rate	3.5% until year 35	According to DMC's methods guide (53)
Intervention	Avapritinib	
Comparator(s)	Established clinical management	Due to the orphan setting and as mentioned in the Danish treatment guidelines there is no effective approved therapy for this small patient population (34). However, it was assumed that the closest to clinical reality the relevant comparator to avapritinib for the proposed indication is that a minority of patients, of 20%, will receive first-line imatinib.

Model features	Description	Justification
		The remaining patients, and patients that progress, receive best supportive care. The other TKIs included in the BLU-285-1002 study and mentioned in the Danish guidelines for GIST are considered to be completely ineffective in mutated patients (34).
Outcomes	OS and PFS as efficacy points	ORR was the primary endpoint in the NAVIGATOR study. OS was explorative endpoint, PFS was secondary endpoint.

Abbreviations: EMA: European Medicines Agency, DMC: Danish Medicines Council, OS: overall survival, PFS: progression-free survival, GIST: gastrointestinal stromal tumor, ORR: objective response rate, TKIs: tyrosine kinase inhibitors

5. Overview of literature

5.1 Literature used for the clinical assessment

A clinical SLR was conducted on 29 June 2023, the full details of which is provided in Appendix H. The SLR search aimed to address the following research question:

- To evaluate and summarise evidence pertaining to the efficacy, safety and tolerability of treatment options used in patients unresectable and/or metastatic GIST harbouring the PDGFRA D842V mutation.

In summary, 42 publications were identified from the clinical SLR, which included 25 unique studies. 4 studies are considered most relevant to include for this submission to inform the comparative analysis of avapritinib vs TKI therapy and are presented in Table 9.

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

A utility SLR was conducted on 23 June 2023, the full details of which is provided in Appendix I. The SLR search aimed to address the following research questions:

- To identify utility values associated with unresectable and/or metastatic GIST harbouring the PDGFRA D842V mutation.

In summary, 0 publications were identified from the utility SLR. Therefore, in order to inform the submission, a targeted literature review was carried out to source utility values from NICE and identified TA86/TA209 (TA209, final appraisal determination papers, point 4.2.13, page 16 of 45; imatinib) (56, 57) and TA179 (final appraisal determination papers, point 3.10, page 7 of 26; sunitinib) (58) will be used to inform the two health states: AVA/1L and SoC1. Furthermore, unpublished data will be used from the VOYAGER trial, applying utility values to two health states: SoC2 and PD. AE utility decrements were also identified from TA790 (TA730, committee papers, Table 49) (59). These studies are described in Table 10.

5.3 Literature used for inputs for the health economic model

At the time of writing this submission dossier, a SLR on health economic models was not conducted in time to accommodate the new DMC submission template. A targeted literature review was performed to identify additional safety data for the comparator arm as well as HCRU and resource use for the model. These are described in Table 11.

Table 9 Relevant studies included in the assessment of efficacy and safety of avapritinib vs TKI therapy in PDGFRA D842 GIST patients

Reference	Trial name	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of
Jones RL et al., 2020. Avapritinib in unresectable or metastatic PDGFRA D842V-mutant gastrointestinal stromal tumours: Long-term efficacy and safety data from the NAVIGATOR phase I trial. Eur J Cancer. 2021 Mar;145:132-142. doi: 10.1016/j.ejca.2020.12.008. Epub 2021 Jan 16. (60) (51)	NAVIGATOR	NCT02508532	Start: 07/10/15 Completion: 03/06/23 Data cut-off: 09/03/20 Future data cut-offs: Completed	Avapritinib
A retrospective natural history study of patients (pts) with PDGFRα D842V mutant advanced gastrointestinal stromal tumor (GIST) previously treated with a tyrosine kinase inhibitor (TKI). Margaret von Mehren et al., 2018. Journal of Clinical Oncology 2018 36:15_suppl, 11533-11533 (61)	BLU-285-1002	Not applicable	Start: January 2000 Completion: July 2016	TKI therapy
von Mehren, M., Heinrich, M.C., Shi, H. et al. Clinical efficacy comparison of avapritinib with other tyrosine kinase inhibitors in gastrointestinal stromal tumors with PDGFRA D842V mutation: a retrospective analysis of clinical trial and real-world data. BMC Cancer 21, 291 (2021). https://doi.org/10.1186/s12885-021-08013-1 (62) (5)	N/A	N/A	N/A	Indirect comparison of avapritinib to TKI therapy
Cassier et al., 2012. Outcome of patients with platelet-derived growth factor receptor alpha-mutated gastrointestinal stromal tumors in the tyrosine kinase inhibitor era (3)	N/A	N/A	N/A	Scenario analysis of BLU-285-1002 IPW results against imatinib. Presented in Appendix C.1.5. Does not inform key efficacy information for this submission, merely supportive in nature.

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

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Kang Y-K, George S, Jones RL, Rutkowski P, Shen L, Mir O, et al. Avapritinib versus regorafenib in locally advanced unresectable or metastatic GI stromal tumor: a randomized, open-label phase III study. Journal of clinical oncology. 2021;39(28):3128-39 (6)	SoC2 and PD utility values	See Section 10
NICE TA86/TA209 (TA209, final appraisal determination papers, point 4.2.13, page 16 of 45; imatinib) (56, 57)	ECOG performance (avapritinib/1L utility value)	See Section 10
NICE TA179 (final appraisal determination papers, point 3.10, page 7 of 26; sunitinib) (58)	SoC1 utility value	See Section 10
NICE TA730 (TA730, committee papers, Table 49) (59).	AE utility decrements	See 10.2.2

Table 11 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Blueprint Medicines Corporation. Indirect comparison for avapritinib in the treatment of gastrointestinal stromal tumors (GIST) with PDGFRA D842V mutation. [Data on file]. 2020. (5)	OS, PFS, ToT	N/A	See section 8.1.1
NAVIGATOR CSR [Data on file] (51)	Safety data for avapritinib	N/A	See section 9.1
Demetri GD, et al 2002. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. New England Journal of Medicine. 2002;347(7):472-80. (63) Demetri GD et al 2006. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. The Lancet. 2006;368(9544):1329-38. (64) Demetri GD et al 2013. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. The Lancet. 2013;381(9863):295-302 (65)	Safety data for imatinib, sunitinib, and regorafenib (ECM)	Targeted literature review	See section 9.2
NICE GIST technology appraisal, TA488 (committee papers, section 2.4)	HCRU cost values and resource use frequencies	Panel of UK clinical experts	See section 11.4

6. Efficacy

6.1 Efficacy of avapritinib compared to TKI therapy for unresectable or metastatic GIST patients harbouring the PDGFRA D842V mutation

6.1.1 Relevant studies

The NAVIGATOR (BLU-285-1101, NCT02508532) study describes the efficacy of avapritinib in unresectable or metastatic GIST patients harbouring the PDGFRA D842V mutation.

The BLU-285-1002 study was only available as an abstract, the full details of the reported efficacy and baseline characteristics could not be extracted and will therefore not be reported (61). However, the comparative analysis described below was still possible, since the authors of the comparative analysis were also the authors of the BLU-285-1002, hence had access to all the relevant data. A brief description of BLU-285-1002 is provided in Appendix C.

Table 12 Overview of study design for studies included in the comparison

Trial name, NCT-number	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
NAVIGATOR (BLU-285-1101) NCT02508532 Jones RL et al., 2021. Avapritinib in unresectable or metastatic PDGFRA D842V-mutant gastrointestinal stromal tumours: Long-term efficacy and safety data from the NAVIGATOR phase I trial. Eur J Cancer. 2021 Mar;145:132-142. doi: 10.1016/j.ejca.2020.12.008. Epub 2021 Jan 16. (60)	Phase I, single arm, open-label, multicentre, dose escalation and dose expansion clinical trial.	5 years	The study was divided into 3 groups: Patients with unresectable GIST that had progressed following treatment with imatinib and at least one of the following: sunitinib, regorafenib, sorafenib, dasatinib, pazopanib, or an experimental tyrosine kinase inhibitor therapy, and who did not have a D842V mutation in PDGFRA (Group 1). Patients with unresectable GIST harbouring a D842V mutation in the PDGFRA gene,	Avapritinib was to be administered PO QD, in the morning, on Days 1 to 28 in 28-day cycles. Dosing was to be continuous, with no inter-cycle rest periods. In Part 2, patients were initially treated at a dose of 400 mg QD. Based on the emerging safety data, the dose utilized for Part 2 was reduced to 300 mg QD. Fifty-six patients with the PDGFRA D842V mutation were treated with avapritinib in Part 2 of the NAVIGATOR study: Seventeen patients were	N/A	Primary outcome measures: Part 1: Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose (RP2D) of Avapritinib[Time Frame: Cycle 1 (28 days) of treatment] Parts 1 and 2: Number of Patients With Adverse Events (AE) and Serious Adverse Events (SAE) [Time Frame: AEs were collected from the start of study drug until 30 days after the last dose, SAEs were collected from the date of the informed consent signature until 30 days after the last dose of study drug, up to 5 years] Part 2: Overall Response Rate (ORR) Determined by Central Radiology Assessment Per mRECIST, Version 1.1 [Time Frame: Tumor assessments were performed at screening, Cycle 3 Day 1, then every 2 cycles through Cycle 13, then every 3 cycles thereafter up to approximately 4 years. Each cycle is 28 days.] Secondary outcome measures: Maximum Plasma Drug Concentration (Cmax) [Time Frame: Cycle 1 Day 1] Time to Maximum Plasma Drug Concentration (Tmax) [Time Frame: Cycle 1 Day 1] Plasma Drug Concentration at 24 Hours Postdose Prior to the Next Daily Dose (C24) [Time Frame: Cycle 1 Day 1] Area Under the Plasma Concentration-time Curve From Time 0 to 24 Hours (AUC 0-24) [Time Frame: Cycle 1 Day 1] Apparent Oral Clearance Unadjusted for Bioavailability (CL/F) [Time Frame: Cycle 1 Day 1] Apparent Volume of Distribution, Unadjusted for Bioavailability (Vz/F) [Time Frame: Cycle 1 Day 1] Terminal Elimination Half-life (t1/2) [Time Frame: Cycle 1 Day 1] Maximum Plasma Drug Concentration (Cmax) at Steady State [Time Frame: Cycle 1 Day 15] Time of Maximal Concentration (Tmax) at Steady State [Time Frame: Cycle 1 Day 15] Plasma Drug Concentration at 24 Hours Postdose Prior to the Next Daily Dose at Steady State (C24,ss) [Time Frame: Cycle 1 Day 15]

Trial name, NCT-number	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
Heinrich MC et al., 2020. Avapritinib in advanced PDGFRA D842V-mutant gastrointestinal stromal tumour (NAVIGATOR): a multicentre, open-label, phase 1 trial. Lancet Oncol. 2020 Jul;21(7):935-946. doi: 10.1016/S1470-2045(20)30269-2. Erratum In: Lancet Oncol. 2020 Sep;21(9):e418. (66)			identified by local and central assessment, either in archival tissue or a new tumour biopsy obtained, prior to treatment with avapritinib (Group 2). Patients with unresectable GIST that had progressed or those who had experienced intolerance following treatment with imatinib (including in the adjuvant setting) and who had not received additional kinase inhibitor therapy and did not have a known D842V mutation in PDGFRA (Group 3)	treated at a dose < 300 mg QD (including starting doses of 30 mg, 60 mg, 90 mg, 135 mg and 200 mg) Twenty-eight patients were treated at a dose of 300 mg QD Ten patients were treated at a dose of 400 mg QD One patient was treated at a dose of 600 mg		Area Under the Plasma Concentration-time Curve Over the Dosing Interval at Steady Sate (AUC0-τ,ss) (τ=24 h) [Time Frame: Cycle 1 Day 15] Progression-free Survival Per mRECIST Version 1.1 [Time Frame: Tumour assessments were performed at screening, Cycle 3 Day 1, then every 2 cycles through Cycle 13, then every 3 cycles thereafter up to approximately 4 years. Each cycle is 28 days.] Apparent Oral Clearance at Steady State, Unadjusted for Bioavailability (CLss/F) [Time Frame: Cycle 1 Day 15] Clinical Benefit Rate Determined by Central Radiology Assessment Per mRECIST, Version 1.1 [Time Frame: Tumour assessments were performed at screening, Cycle 3 Day 1, then every 2 cycles through Cycle 13, then every 3 cycles thereafter up to approximately 4 years. Each cycle is 28 days.] Response Rate Determined by Central Radiology Assessment Per Choi Criteria [Time Frame: Tumour assessments were performed at screening, Cycle 3 Day 1, then every 2 cycles through Cycle 13, then every 3 cycles thereafter up to approximately 4 years. Each cycle is 28 days.] Duration of Response Determined by Central Radiology Assessment Per mRECIST, Version 1.1 [Time Frame: Tumour assessments were performed at screening, Cycle 3 Day 1, then every 2 cycles through Cycle 13, then every 3 cycles thereafter up to approximately 4 years. Each cycle is 28 days.] Median PFS on Last Prior Anti-cancer Therapy [Time Frame: Historical data collected at enrolment, all available data on prior therapy was collected] Change From Baseline in Levels of KIT and PDGFRα Mutant Allele Fractions in Peripheral Blood [Time Frame: Baseline and End of treatment] KIT, PDGFRA, and Other Cancer-relevant Mutations Present in Tumour Tissue at Baseline and EOT [Time Frame: Baseline and end of treatment]

6.1.2 Comparability of studies

The NAVIGATOR and BLU-285-1002 studies are similar in that they both report OS and PFS as efficacy outcomes using the same definition (RECIST). However, BLU-285-1002 included patients with localised GIST, whereas NAVIGATOR included patients with unresectable or metastatic GIST, a key prognostic factor in this case since treatment pathways are very different. To account for this, patients from BLU-285-1002 with localised GIST were excluded from the analysis, the full details of which are described in Section 7.

6.1.2.1 Comparability of patients across studies

Table 13 provides the key baseline characteristics (both weighted and unweighted) with key confounding factors for the NAVIGATOR and BLU-285-1002 studies. Baseline characteristics were compared using the chi-square test (62) and the standard difference (SD) (both weighted and unweighted) based on the prevalence between groups (67, 68). Please refer to Section 7 for further details.

Table 13 Baseline characteristics for the NAVIGATOR study and BLU-285-1002 (at time of first TKI for unresectable or metastatic disease) presenting key confounding factors

		NAVIGATOR N = 56		BLU-285-1002 N = 19				
Factors	**UW Total (n,%)**	**UW (n,%)**	**W (n,%)**	**UW (n,%)**	**W (n,%)**	**p-value**	**UW SD**	**W SD**
Sex						0.601		
• Male	51 (68.0)	39 (69.6)	37 (66.3)	12 (63.2)	11 (57.1)		0.136	0.190
• Female	24 (32.0)	17 (30.4)	19 (33.7)	7 (36.8)	8 (42.9)		0.136	0.190
Age						0.046*		
• < 60 years	29 (38.7)	18 (32.1)	21 (37.6)	11 (57.9)	6 (30.7)		0.537	0.146
• ≥ 60 years	46 (61.3)	38 (67.9)	35 (62.4)	8 (42.1)	13 (69.3)		0.537	0.146
Race						0.101		
• White	57 (82.6)	39 (78.0)	39 (69.4)	18 (94.7)	18 (97.1)		0.501	0.799
• Non-white	12 (17.4)	11 (22.0)	17 (30.6)	1 (5.3)	1 (2.9)		0.501	0.799
• Missing	6	6	-	0	-		N/A	N/A
Anatomical site						0.757		
• Gastric (stomach)	61 (81.3)	46 (82.1)	46 (81.9)	15 (79.0)	17 (88.7)		0.078	0.193
• Small bowel or rectal (any	14 (18.7)	10 (17.9)	10 (18.1)	4 (21.0)	2 (11.3)		0.078	0.193

		NAVIGATOR N = 56		BLU-285-1002 N = 19				
Factors	UW Total (n,%)	UW (n,%)	W (n,%)	UW (n,%)	W (n,%)	p-value	UW SD	W SD
other organ)								
Metastatic disease						0.745		
• No	3 (4.0)	2 (3.6)	2 (4.0)	1 (5.3)	1 (3.2)		0.083	0.043
• Yes	72 (96.0)	54 (96.4)	54 (96.0)	18 (94.7)	18 (96.8)		0.083	0.043
ECOG performance status						0.445		
• 0	22 (38.6)	21 (37.5)	-	1 (100.0)	-		1.826	N/A
• 1	32 (56.1)	32 (57.1)	-	0 (0.0)	-		1.632	N/A
• 2+	3 (5.3)	3 (5.4)	-	0 (0.0)	-		0.338	N/A
• Missing	18	0	-	18	-			
Duration of disease						0.386		
• < 3 years	45 (60.0)	32 (57.1)	33 (58.8)	13 (68.4)	9 (45.9)		0.235	0.260
• ≥ 3 years	30 (40.0)	24 (42.9)	23 (41.2)	6 (31.6)	10 (54.1)		0.235	0.260
Number of total TKI						0.124		
• 1	14 (18.7)	11 (19.6)	9 (16.9)	3 (15.8)	9 (46.8)		0.100	0.678
• 2	26 (34.7)	23 (41.1)	22 (39.0)	3 (15.8)	3 (15.7)		0.584	0.542
• 3	13 (17.3)	9 (16.1)	11 (18.8)	4 (21.0)	3 (13.7)		0.126	0.139
• 4+	22 (29.3)	13 (23.2)	14 (25.4)	9 (47.4)	5 (23.8)		0.523	0.037

Abbreviations: ECOG = Eastern Cooperative Oncology Group; SD = standard difference; TKI = tyrosine kinase inhibitor; UW = unweighted; W = weighted.

Notes: *, p-value was statistically significant ($p \leq 0.05$).

Source: Clinical efficacy comparison (62)

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

Due to the orphan nature of the disease, very little is known about the patient characteristics in Danish clinical practice. The best sources are only available from the Danish clinical guidelines (34).

Table 14 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (reference)	Value used in health economic model (reference if relevant)
Age (mean)	65 (34)	61.70 (60)
Male	50% (34)	65.8% (60)

6.1.4 Efficacy – NAVIGATOR (BLU-285-1101, NCT02508532)

Evidence for the key outcomes from the NAVIGATOR study in the unresectable or metastatic GIST population with the PDGFRA D842V mutation are presented in the sections below. The licensed dose for this indication is to be 300 mg once daily; however, no differences in efficacy outcomes were evident between the groups receiving the 300 mg and 400 mg doses (51), therefore, these groups were analysed together to provide the evidence for the Market Authorisation Application submission to the EMA. This will be presented as the 300 mg/400 mg population (N=38) and is the main efficacy population. In addition, as the underlying efficacy of the health economic model and comparative analysis is based on the PDGFRA D842V patients who received all doses of avapritinib from the NAVIGATOR study (N=56), this will also be presented alongside the 300 mg/400 mg population to ensure transparency of all results.

The primary data sources for the NAVIGATOR study that are presented in this submission is the clinical study report (CSR) which contains 2 data cuts (DC):

- January 2021 DC was done for overall survival and safety only and will be presented below (median follow-up of 33.1 and 36.3 months for PDGFRA D842V mutation population receiving 300/400 mg and all doses of avapritinib respectively) (51)
- March 2020 DC was done for overall response rate, duration of response, time to response, progression-free survival and radiographic tumour reductions (median follow-up of 25.5 months for PDGFRA D842V mutation population receiving 300/400 mg and all doses of avapritinib) (51)

6.1.4.1 Overall response rate (March 2020 DC)

Overall response rate (ORR) was the primary endpoint for the NAVIGATOR study (51). The latest ORR efficacy results are based on the March 2020 DC. Table 15 presents the response rates from the NAVIGATOR study. Almost all patients with the PDGFRA D842V mutation treated with 300 mg/400 mg and all doses of avapritinib achieved a clinic response – the ORR was 94.7% and 91.1% respectively (51).

The CBR and DCR are important outcomes for patients with unresectable or metastatic PDGFRA D842V-mutated GIST (51). Given the lack of alternative effective treatment options, avoiding PD for a longer period is likely to result in substantially better outcomes. In the NAVIGATOR study, the DCR for avapritinib-treated patients with the PDGFRA D842V mutation was an unprecedented 100%, showing that no patients went straight to PD. The CBR was 97.4% and 98.2% for the 300 mg/400 mg and all doses patient groups respectively (51).

Table 15 Summary of best response[a] of unresectable or metastatic GIST patients with PDGFRA D842V mutation; NAVIGATOR; March 2020 DC

Parameters	Avapritinib (300 mg/400 mg) N = 38	Avapritinib (All doses) N = 56
ORR, [b] n (%, 95% Cic)	36 (94.7, 82.3–99.4)	51 (91.1, 80.4-97.0)
CR, n (%, 95% CI)	5 (13.2, 4.4–28.1)	7 (12.5, N/A)
PR, n (%, 95% CI)	31 (81.6, 65.7–92.3)	44 (78.6, N/A)
SD, n (%, 95% CI)	2 (5.3, 0.6–17.7)	5 (8.9, N/A)
PD, n (%)	0 (0)	0 (0)
CBR, d n (%, 95% Cic)	37 (97.4, 86.2–99.9)	55 (98.2, 90.4-100.0)
DCR, e n (%, 95% CI)	38 (100.0, 90.7–100.0)	56 (100, 93.6-100.0)
Median DOR, months (95% CI)	22.1 (14.1–NE)	27.3 (17.6-32.2)

Abbreviations: CBR = clinical benefit rate; CI = confidence interval; CR = complete response; DCR = disease control rate; DOR = duration of response; mRECIST = modified Response Evaluation Criteria in Solid Tumours; N/A = not available; ORR = overall response rate; PD = progressive disease; PDGFRA = platelet-derived growth factor receptor alpha; PR = partial response; SD = stable disease.

Notes: [a] best response assessed by central radiology using mRECIST Version 1.1; [b], the proportion of patients with a confirmed best response of CR or PR; [c], two-sided 95% CI based on exact binomial distribution using the Clopper–Pearson method; [d], the proportion of patients with confirmed CR/PR or SD lasting ≥4 cycles from first dose date; [e], the proportion of patients with a confirmed best response of CR, PR, or SD.

Source: NAVIGATOR CSR; Table 14.2.1.1.2 (51)

6.1.4.2 Duration of response (March 2020 DC)

The latest DOR results are based on the March 2020 DC. The median DOR was 22.1 and 27.3 months for patients with the PDGFRA D842V mutation who were treated with 300 mg/400 mg and all doses of avapritinib respectively (51). Table 16 provides an overview of the results from the NAVIGATOR study. The Kaplan-Meier curve for DOR is presented in Figure 2 & Figure 3 for both patient groups.

Table 16 DOR by central radiology per mRECIST 1.1 and EMA Censoring Rule of unresectable or metastatic GIST patients with PDGFRA D842V mutation; NAVIGATOR; March 2020 DC

Duration of response	Avapritinib (300 mg/400 mg) N = 36	Avapritinib (All doses) N = 51
Patients with events, n (%)	19 (52.8)	26 (51.0)

Patients censored, n (%)	17 (47.2)	25 (49.0)
Kaplan-Meier estimates		
Median (95% CI)	22.1 (14.1, -)	27.3 (17.6-32.2)
25th, 75th percentile	11.5, -	11.5, -
• 3 months (95% CI)	100 (100.0, 100.0)	98.0 (94.1, 100.0)
• 6 months (95% CI)	88.6 (78.0, 99.1)	86.0 (76.4, 95.6)
• 9 months (95% CI)	82.9 (70.4, 95.3)	81.8 (71.0, 92.6)
• 12 months (95% CI)	74.2 (59.6, 88.7)	73.3 (60.8, 85.8)
• 18 months (95% CI)	58.8 (42.2, 75.5)	61.9 (48.0, 75.9)
• 24 months (95% CI)	43.3 (25.2, 61.3)	51.3 (36.3, 66.3)
• 30 months (95% CI)	32.5 (9.6, 55.3)	37.3 (19.9, 54.6)
• 36 months (95% CI)	32.5 (9.6, 55.3)	29.8 (10.8, 48.9)

Abbreviations: CI = confidence interval; CR = complete response; EMA = European Medicines Agency; mRECIST = modified Response Evaluation Criteria in Solid Tumours; PDGFRA = platelet-derived growth factor receptor alpha; PR = partial response.

Notes: Duration of Response is defined as the time in months from first documented response (CR/PR) to the date of first documented disease progression or death due to any cause, whichever comes first. Patients without confirmed CR or PR will be excluded from this analysis. Patients who are still in response at time of data cutoff will be censored at their last valid assessment. Confidence intervals are calculated using the linear transformation.

Source: NAVIGATOR CSR; Table 14.2.2.2.2 (51)

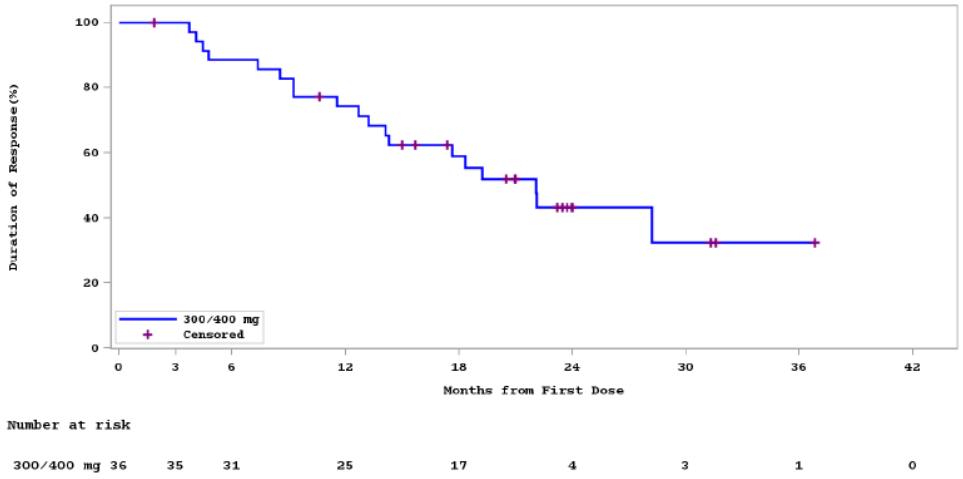

Figure 2 Kaplan-Meier curve of DOR per EMA censoring rule of unresectable or metastatic GIST patients with PDGFRA D842V mutation; 300/400 mg dose; NAVIGATOR; March 2020 DC

Abbreviations: EMA = European Medicines Agency; PDGFRA = platelet-derived growth factor receptor alpha.

Notes: DOR is defined as the time in months from first documented response (CR/PR) to the date of first documented disease progression or death due to any cause, whichever comes first. Patients without confirmed CR or PR will be excluded from this analysis. Patients who are still in response at time of data cutoff will be censored at their last valid assessment. Product-limit method used to obtain Kaplan-Meier estimates of survival.

Source: NAVIGATOR CSR; Figure 15.2.2.2.2; 300/400 mg (51)

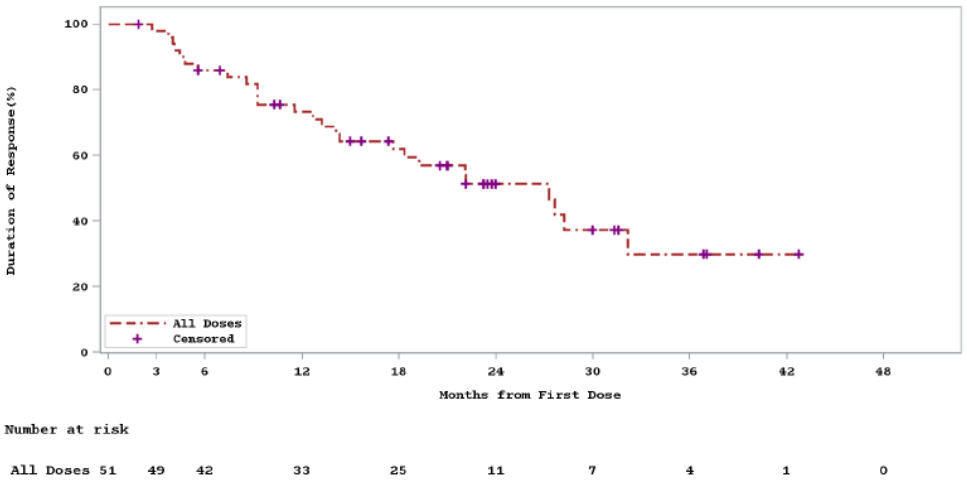

Figure 3 Kaplan-Meier curve of DOR per EMA censoring rule of unresectable or metastatic GIST patients with PDGFRA D842V mutation; all doses; NAVIGATOR; March 2020 DC

Abbreviations: EMA = European Medicines Agency; PDGFRA = platelet-derived growth factor receptor alpha.

Notes: DOR is defined as the time in months from first documented response (CR/PR) to the date of first documented disease progression or death due to any cause, whichever comes first. Patients without confirmed CR or PR will be excluded from this analysis. Patients who are still in response at time of data cutoff will be censored at their last valid assessment. Product-limit method used to obtain Kaplan-Meier estimates of survival.

Source: NAVIGATOR CSR; Figure 15.2.2.2.2; all doses (51)

6.1.4.3 Time to response (March 2020 DC)

The latest time to response results is based on the March 2020 DC. The median time to response was 59.5 and 61.0 days for patients with the PDGFRA D842V mutation who were treated with 300 mg/400 mg and all doses of avapritinib respectively (51). Table 17 provides an overview of the results from the NAVIGATOR study. The results were consistent across all dose groups (51).

Table 17 Time to response by central radiology per mRECIST 1.1 of unresectable or metastatic GIST patients with PDGFRA D842V mutation; NAVIGATOR; March 2020 DC

Time to response	Avapritinib (300 mg/400 mg) N = 36	Avapritinib (All doses) N = 51
Time to first response (CR/PR) Median (range), days	59.5 (52-757)	61.0 (52-757)

Abbreviations: CR = complete response; mRECIST = modified Response Evaluation Criteria in Solid Tumours; PDGFRA = platelet-derived growth factor receptor alpha; PR = partial response.

Notes: Time to response is defined as the time in days from the start of treatment to the time the response criteria for CR or PR are first met per mRECIST Version 1.1. Patients without confirmed CR or PR will be excluded from this analysis.

Source: NAVIGATOR CSR; Table 14.2.2.9.2 (51)

6.1.4.4 Overall survival (January 2021 DC)

OS was an explorative endpoint for the NAVIGATOR study (51). The latest OS efficacy results are based on the January 2021 DC. Table 18 presents the OS results from the NAVIGATOR study. Among the patients with the PDGFRA D842V mutation treated with the 300 mg/400 mg and all doses of avapritinib, median follow-up was 33.1 and 36.3 months respectively. Median survival was not reached in both patient groups (51). The Kaplan-Meier curves for OS is presented in Figure 4 and Figure 5 for both patient groups.

Table 18 Summary of OS unresectable or metastatic GIST patients with PDGFRA D842V mutation; NAVIGATOR; January 2021 DC

Kaplan-Meier estimates[a]	Avapritinib (300 mg/400 mg) N = 38	Avapritinib (All doses) N = 56
Median (95% CI)	Not reached	Not reached
• 6 months (95% CI)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)
• 12 months (95% CI)	91.4 (82.2, 100.0)	92.5 (85.3, 99.6)
• 18 months (95% CI)	88.6 (78.0, 99.1)	88.7 (80.1, 97.2)
• 24 months (95% CI)	71.0 (55.9, 86.2)	75.3 (63.6, 87.0)
• 30 months (95% CI)	71.0 (55.9, 86.2)	69.0 (56.4, 81.7)
• 36 months (95% CI)	71.0 (55.9, 86.2)	65.8 (52.1, 79.4)
• 42 months (95% CI)	63.1 (43.3, 83.0)	62.1 (47.5, 76.7)

Abbreviations: CI = confidence interval; PDGFRA = platelet-derived growth factor receptor alpha.

Notes: OS was defined as the time from the start of treatment to the date of death. All patients who did not have a death record prior to or on the cut-off date were censored at either the data cut-off date or the last date known alive + 1, whichever occurred earlier. [a], Kaplan–Meier estimates with censoring at the earlier of the data cut-off date and the last date known alive + 1.

Source: NAVIGATOR CSR; Table 14.2.4.1.2 (51)

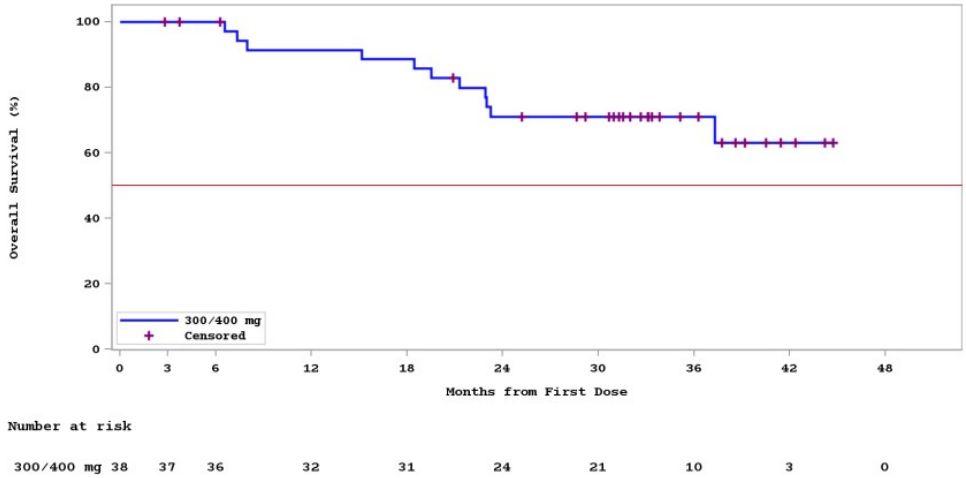

Figure 4 Kaplan-Meier curve of OS of unresectable or metastatic GIST patients with PDGFRA D842V mutation; NAVIGATOR; 300/400 mg; January 2021 DC

Abbreviations: PDGFRA = platelet-derived growth factor receptor alpha.

Source: NAVIGATOR CSR; Figure 15.2.4.1.2; 300/400 mg (51)

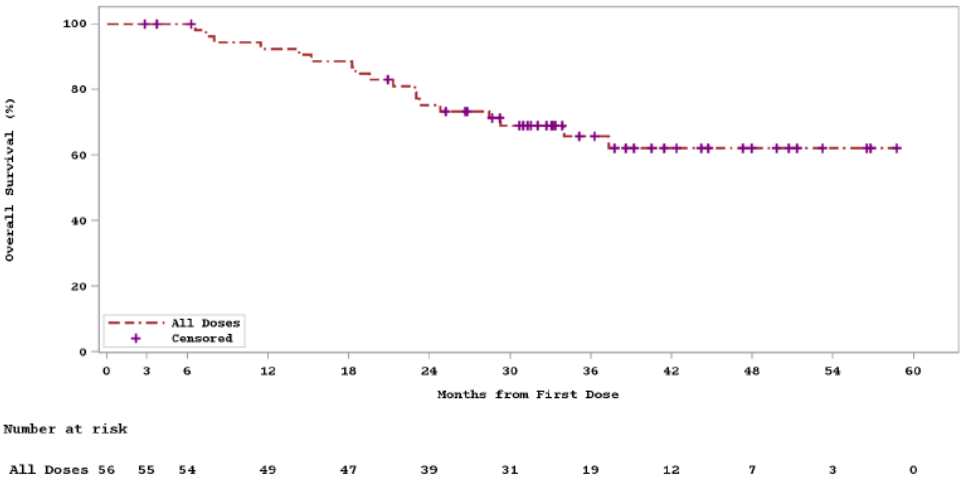

Figure 5 Kaplan-Meier curve of OS of unresectable or metastatic GIST patients with PDGFRA D842V mutation; NAVIGATOR; all doses; January 2021 DC

Abbreviations: PDGFRA = platelet-derived growth factor receptor alpha.

Source: NAVIGATOR CSR; Figure 15.2.4.1.2; all doses (51)

6.1.4.5 Progression-free survival (March 2020 DC)

PFS was a secondary endpoint for the NAVIGATOR study (51). The latest PFS efficacy results are based on the March 2020 DC. Table 19 presents the PFS results from NAVIGATOR study. Among the patients with the PDGFRA D842V mutation treated with the 300 mg/400 mg and all doses of avapritinib, median PFS was 24.0 and 29.2 months respectively (51). The Kaplan-Meier curve for PFS is presented in Figure 6 and Figure 7 for both patient groups.

Table 19 Summary of PFS per EMA censoring rule of unresectable or metastatic GIST patients with PDGFRA D842V mutation; NAVIGATOR; March 2020 DC

Kaplan-Meier estimates	Avapritinib (300 mg/400 mg) N = 38	Avapritinib (All doses) N = 56
Median (95% CI)	24.0 (18.4, -)	29.2 (22.9,-)
• 6 months (95% CI)	94.3 (86.6, 100.0)	92.5 (85.3, 99.6)
• 12 months (95% CI)	82.9 (70.4, 95.3)	83.0 (72.9, 93.1)
• 18 months (95% CI)	68.6 (53.2, 84.0)	71.7 (59.6, 83.8)
• 24 months (95% CI)	53.4 (36.6, 70.2)	61.5 (48.2, 74.8)
• 30 months (95% CI)	42.7 (23.2, 62.3)	45.4 (29.6, 61.1)
• 36 months (95% CI)	34.2 (12.5, 55.8)	37.2 (20.6, 53.8)

Abbreviations: CI = confidence interval; EMA = European Medicines Agency; PDGFRA = platelet-derived growth factor receptor alpha.

Notes: PFS is defined as the time in months from the start of treatment to the date of first documented disease progression or death due to any cause, whichever occurs first. If a patient has not had an event, PFS is censored at the date of last valid assessment that is stable or better. Confidence intervals are calculated using the linear transformation.

Source: NAVIGATOR CSR; Table 14.2.3.2.2 (51)

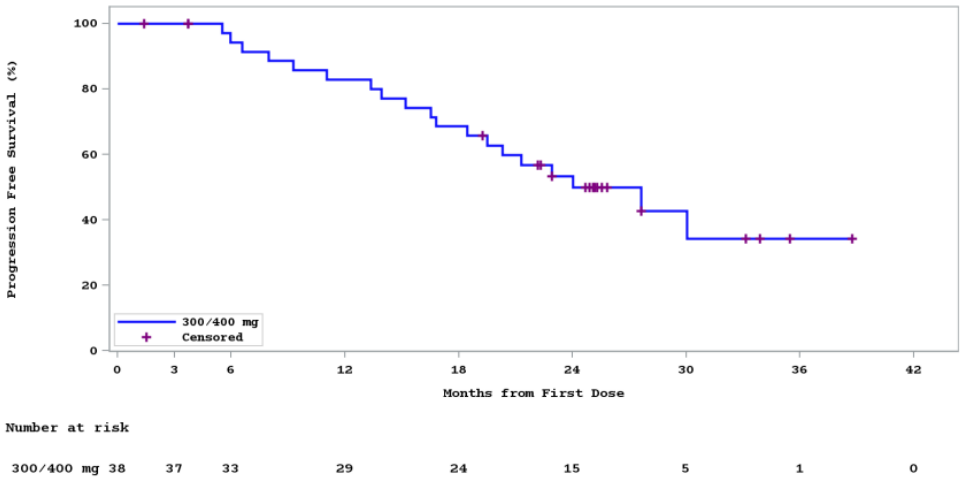

Figure 6 Kaplan-Meier curve of PFS per EMA censoring rule of unresectable or metastatic GIST patients with PDGFRA D842V mutation; NAVIGATOR; 300/400mg; March 2020 DC

Abbreviations: EMA = European Medicines Agency; PDGFRA = platelet-derived growth factor receptor alpha.

Source: NAVIGATOR CSR; Figure 15.2.3.2.2; 300/400 mg (51)

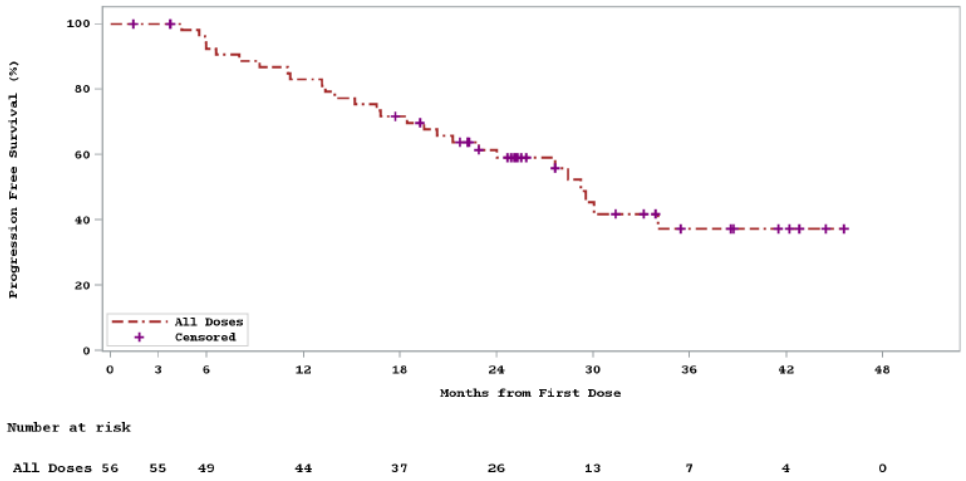

Figure 7 Kaplan-Meier curve of PFS per EMA censoring rule of unresectable or metastatic GIST patients with PDGFRA D842V mutation; NAVIGATOR; all doses; March 2020 DC

Abbreviations: EMA = European Medicines Agency; PDGFRA = platelet-derived growth factor receptor alpha.

Source: NAVIGATOR CSR; Figure 15.2.3.2.2; all doses (51)

6.1.4.6 Radiographic tumour reductions (March 2020 DC)

The latest radiographic tumour reductions results are based on the March 2020 DC. Radiographic tumour reductions by mRECIST 1.1 criteria were observed in 94.7% of patients with the PDGFRA D842V mutation who were treated with 300 mg/400 mg of avapritinib in the NAVIGATOR study (Figure 8) (51). Four patients with 100% reduction in tumour size did not have a CR per central radiology assessment: one due to an increase in ascites, one who had no confirmatory scan available, and one due to persistent non-target lesions (51). The high proportion of patients with a response and the high percentage of reduction in tumour sizes are extremely positive outcomes for patients in this population.

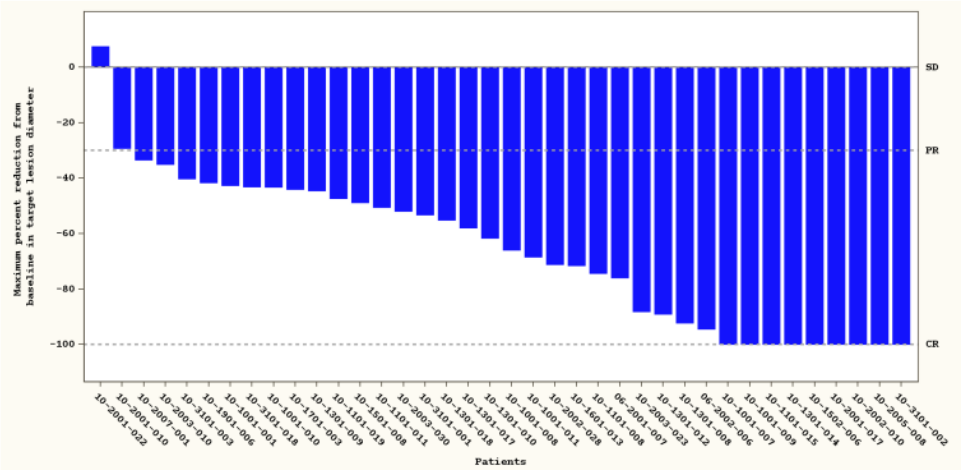

Figure 8 Waterfall plot of sum of diameter of target lesion by central radiology per mRECIST 1.1 of unresectable or metastatic GIST patients with PDGFRA D842V mutation; NAVIGATOR; March 2020 DC

Abbreviations: CR = complete response; EMA = European Medicines Agency; mRECIST = modified Response Evaluation Criteria in Solid Tumours; PD = progressive disease; PDGFRA = platelet-derived growth factor receptor alpha; PR = partial response; SD = stable disease.

Source: NAVIGATOR CSR; Figure 15.2.1.2.2; 300/400 mg (51)

7. Comparative analyses of efficacy

To inform the comparative analyses between avapritinib and TKI therapy for unresectable or metastatic GIST patients harbouring the PDGFRA D842V mutation, an indirect comparison using inverse probability weighting (IPW) was done between PDGFRA D842V population in the NAVIGATOR study (60) and BLU-285-1002 (61), details of which has been described in Appendix C. Patients in BLU-285-1002 received ECM, which consists of TKI therapy, including imatinib, sunitinib and regorafenib.

The indirect comparison included the PDGFRA D842V mutation population who received all doses of avapritinib (N = 56) from the NAVIGATOR study (62). The outcomes described are OS and PFS, both of which are based on the latest DCs described above (62). The efficacy outcomes of the indirect comparison are also used in the health economic analysis.

7.1.1 Differences in definitions of outcomes between studies

The primary and secondary endpoints of the indirect comparison were OS and PFS, which was assessed with RECIST 1.1 in BLU-285-1002 and in NAVIGATOR by RECIST 1.1 with modifications for GIST (61).

Given unresectable or metastatic disease is a major driver of prognosis in GIST, the most appropriate approach was to compare results from NAVIGATOR to data from the first TKI for unresectable or metastatic disease in BLU-285-1002. A review of the medical history for all 22 patients in BLU-285-1002 was conducted, with the specific objective of identifying the first TKI received by each patient to treat unresectable or metastatic disease. In most cases, the first TKI for unresectable or metastatic disease was not the first TKI that patients had received in BLU-285-1002, meaning that the patient received previous lines as adjuvant therapy (62).

7.1.2 Method of synthesis

A full description of the methods used for this analysis are presented in Appendix C. Unadjusted comparisons between the NAVIGATOR study and BLU-285-1002 were performed using log-rank tests, which showed that the differences between the outcomes were not due to chance. Therefore, it is appropriate to perform adjusted analysis to account for differences in confounding factors. The results of these unadjusted comparisons and the log-rank test results are presented in Appendix C.

A propensity score weighting analysis was also undertaken; the results of BLU-285-1002 and the NAVIGATOR study were weighted based on their patient characteristics to allow

for the fairest possible comparison of treatment outcomes for avapritinib vs ECM in the patient population with unresectable or metastatic PDGFRA D842V-mutated GIST (62).

As previously discussed, the comparison was performed using data for the first TKI received for unresectable or metastatic disease in BLU-285-1002. For this reason, the patient characteristics from BLU-285-1002 are presented from the start of the first TKI for unresectable or metastatic disease. Similarly, Kaplan–Meier survival functions for OS and PFS from BLU-285-1002 are presented from the initiation of the first TKI for unresectable or metastatic disease (62). Due to this change in the reference timepoint, the patient characteristics, as well as OS and PFS reported in this analysis, do not match what was previously published for BLU-285-1002 (where the reference point was the absolute first TKI) (69). It is also worth noting that three patients from BLU-285-1002 were excluded in the analysis presented here because they received just one TKI for adjuvant treatment before reaching the unresectable or metastatic stage; it would therefore have been inappropriate to include data for these patients (62).

7.1.2.1 Confounding factors

Based on the scientific literature and on the comparable variables available for both studies, some factors potentially associated with the outcome have been identified. The distribution of these factor in the case (NAVIGATOR, avapritinib all doses) and control (BLU-285-1002, TKI therapy (ECM)) group is analysed in terms of absolute numbers and relative frequencies (percentages) and it is compared using chi-square test (62) and the standard difference (SD) (both weighted and unweighted) based on the prevalence between groups (67, 68).

Table 20 summarises the confounding factors used in the analysis. Age, metastatic disease and ECOG performance status were estimated at the start of the reference treatment, while the anatomical site of the primary tumour was recorded at the primary diagnosis. The duration of the disease was estimated from the date of diagnosis to the date of start of reference treatment. The number of TKIs was counted from the first TKI for treatment of unresectable or metastatic disease.

Table 20 Confounding factors

Parameter	Categorisation
Sex	Male/Female
Age	< 60 y/≥ 60 y
Race	White/Non white
Anatomical site of primary tumour	Gastric/Small bowel or rectal
Metastatic disease	Yes/No
ECOG performance status	0 / 1 / 2+
Duration of disease	< 3 y/≥ 3 y
Number of total TKIs* (including avapritinib)	1 / 2 / 3 / 4+

Abbreviations: ECOG = Eastern Cooperative Oncology Group; TKI = tyrosine kinase inhibitor.

Notes: *, counting from the first TKI for treatment of unresectable or metastatic disease.

Source: Clinical efficacy comparison (62)

The results of the comparison of baseline characteristics between NAVIGATOR and BLU-285-1002 and the resulting confounders have previously been presented in Table 13.

7.1.2.2 Inverse probability weighting

Propensity score method was used to adjust for imbalances in the characteristics of the two groups of patients from NAVIGATOR and BLU-285-1002. Considering the low number of patients, the propensity score weighting method is preferred to propensity score matching. A multivariate logistic regression model is used to generate the propensity score indicating the probability of being assigned to cases rather than controls. All the available covariates are included to this model, following the recommendations on propensity score analysis. Weights calculated are used to estimate inverse probability-weighted survival functions, to repeat the comparison between NAVIGATOR and Study 1002 after adjusting for confounding factors.

Calculated weights were generated using a propensity score multivariate logistic regression model. The rationale for the model specification was to include all available parameters that did not have a large proportion of missing data. In doing so, all available information from patients were used to estimate propensity scores. The following parameters were included in the model specification (62):

Gender; age at the start of reference treatment; anatomical site of primary tumour at diagnosis; metastatic disease at start of reference treatment; duration of disease, from diagnosis to start of reference treatment and number of TKIs (counting from the first TKI for treatment of unresectable or metastatic disease).

ECOG performance status and race were not included due to a relatively high number of missing values (62).

The regression results are reported in Table 21. The IPTW distribution is provided in Appendix C.1.5.

Table 21 Results from the propensity score logistic regression

	Coefficient	SE	z	P>z	95% CI	
gender	–0.31392	0.607462	–0.52	0.605	–1.504525	0.8766827
age_dummy	1.0009	0.58709	1.7	0.088	–0.1497757	2.151575
anatomical_site	–0.06337	0.762166	–0.08	0.934	–1.55719	1.430447
metastatic_disease	–0.33643	1.311534	–0.26	0.798	–2.906985	2.234134
total_tki_dummy	–0.48601	0.27785	–1.75	0.08	–1.030588	0.0585652
duration_dummy	0.670031	0.636047	1.05	0.292	–0.5765985	1.916661

_cons	0.751135	2.016702	0.37	0.71	–3.201528	4.703797

Abbreviations: CI = confidence interval; SE = standard error.

Source: Clinical efficacy comparison (62)

7.1.3 Results from the comparative analysis

Table 22 presents the IPW-adjusted Kaplan-Meier survival estimates for OS and PFS of avapritinib vs ECM based on the NAVIGATOR and BLU-285-1002 studies. Further details are presented in the next sections.

Table 22 Results from the comparative analysis of avapritinib (NAVIGATOR) vs. ECM (BLU-285-1002) for unresectable or metastatic GIST patients with PDGFRA D842V mutation

Outcome measure	Avapritinib (N=56)	ECM (N=19)
Overall survival		
Kaplan-Meier survival estimates		
• Median, months	Not reached	12.6
• 6 months	100%	56%
• 12 months	93%	50%
• 18 months	89%	41%
• 24 months	77%	38%
Progression-free survival		
Kaplan-Meier survival estimates		
• Median, months	29.5	3.4
• 6 months	93%	9%
• 12 months	84%	6%
• 18 months	72%	6%
• 24 months	63%	6%

Abbreviations: ECM = established clinical management.

Source: Weighted comparison of BLU-285-1002 and the NAVIGATOR study (5)

7.1.4 Efficacy – Overall survival

The proportions of patients alive at 6, 12, 18, and 24 months for patients treated with avapritinib or ECM are reported in Table 22. Figure 9 presents the IPW-adjusted Kaplan–Meier survival functions for OS in the NAVIGATOR study and BLU-285-1002. The median OS in BLU-285-1002 was 12.6 months; in contrast, median OS was not reached in the NAVIGATOR study (5). Based on the Cox regression analysis, a statistically significant difference (P = 0.0001) between the overall survival curves was demonstrated, favouring avapritinib compared to other TKIs (5).

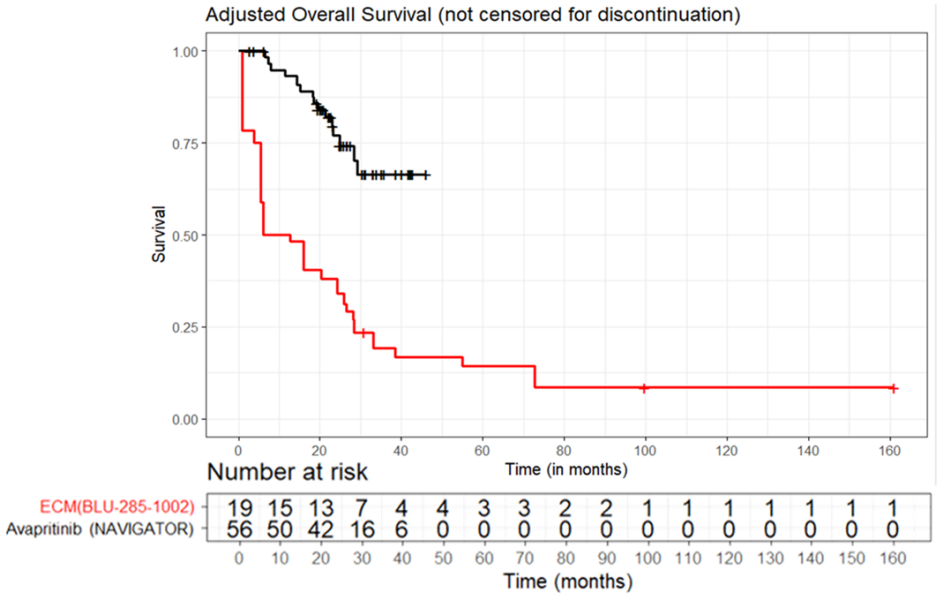

Figure 9 IPW-adjusted Kaplan-Meier curves of OS for avapritinib (NAVIGATOR) and ECM (BLU-285-1002)

Abbreviations: ECM = established clinical management; IPW = inverse probability weighting; TKI = tyrosine kinase inhibitor.

Source: Weighted comparison of BLU-285-1002 and the NAVIGATOR study (5)

The comparison between the two IPW-adjusted survival curves was performed using the Cox regression-based test for equality (Table 23) to test the null hypothesis that there is no difference between the population survival curves. Under the null hypothesis, the risk of death (number of deaths/number alive) from the combined data for both groups were calculated. The result was significant, so the null hypothesis can be rejected, and we can say that the differences observed between the two survival curves are considered not due to chance (5).

Table 23 Cox regression-based test for equality of overall survival curves

Treatment	Events observed	Events expected	Relative hazard
Other TKIs	77.53	48.31	2.0936
Avapritinib	18.61	47.83	0.4742
Total	96.14	96.14	1.0000
X2 = 15.14			
Probability > X2 = 0.0001			

Abbreviations: X2 = chi squared; TKI = tyrosine kinase inhibitor.

Source: Weighted comparison of BLU-285-1002 and the NAVIGATOR study (5)

7.1.5 Efficacy – Progression-free survival

The proportions of patients alive and progression free at 6, 12, 18, and 24 months for patients treated with avapritinib or ECM are reported in Table 22. The IPW-adjusted

Kaplan–Meier survival functions for PFS in the NAVIGATOR study and BLU-285-1002 are reported in Figure 10. The median PFS in BLU-285-1002 was 3.4 months; in contrast, median PFS was 29.5 months in the NAVIGATOR study (5). Based on the Cox regression analysis, a statistically significant difference (P < 0.00001) between the progression-free survival curves was demonstrated, favouring avapritinib compared to other TKIs (5).

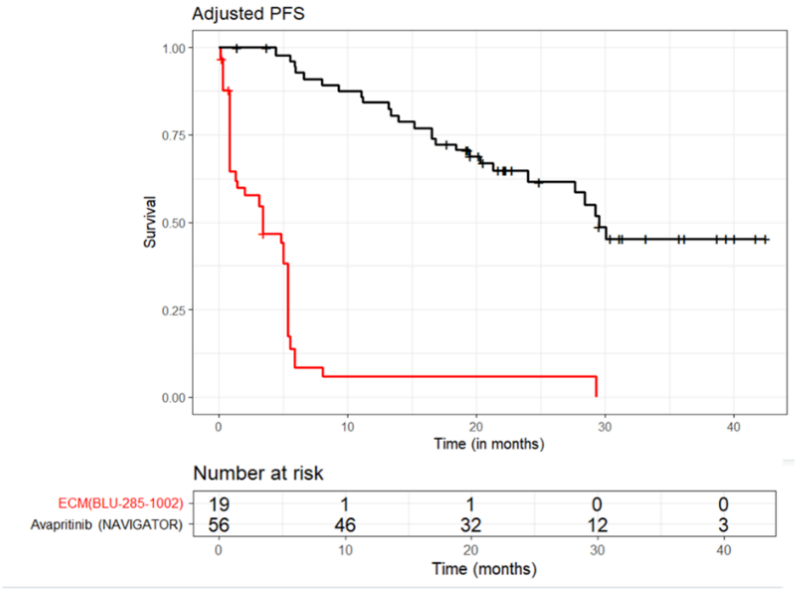

Figure 10 IPW-adjusted Kaplan-Meier curves of PFS for avapritinib (NAVIGATOR) and ECM (BLU-285-1002)

Abbreviations: ECM = established clinical management; IPW = inverse probability weighting; TKI = tyrosine kinase inhibitor.

Source: Weighted comparison of BLU-285-1002 and the NAVIGATOR study (5)

The comparison between the two IPW-adjusted survival curves was performed using the Cox regression-based test for equality (Table 24) to test the null hypothesis that there is no difference between the population survival curves. Under the null hypothesis, the risk of death (number of deaths/number alive) from the combined data for both groups were calculated. The result is significant, so the null hypothesis was rejected, and we can say that the differences observed between the two survival curves are not due to chance (5).

Table 24 Cox regression-based test for equality of progression-free survival curves

Treatment	Events observed	Events expected	Relative hazard
Other TKIs	76.13	30.46	5.5587
Avapritinib	23.70	69.37	0.4708
Total	99.83	99.83	1.0000
X2 = 28.74			
Probability > X2 = 0.0000			

Abbreviations: X2 = chi squared; TKI = tyrosine kinase inhibitor.

Source: Weighted comparison of BLU-285-1002 and the NAVIGATOR study (5)

8. Modelling of efficacy in the health economic analysis

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

As previously described, the NAVIGATOR study is a single-arm clinical study. Therefore, no direct head-to-head evidence to compare the clinical efficacy of avapritinib and ECM was available in this orphan disease, hence an ITC has been conducted to enable an assessment of the relative efficacy between avapritinib and chosen comparator. The key efficacy inputs in the model are PFS and OS. The analysis utilized patient-level data from two specific datasets, namely the NAVIGATOR and BLU-285-1002 (5). To address any variations in baseline characteristics, IPW was applied.

8.1.1 Extrapolation of efficacy data

The OS for avapritinib was generated by fitting parametric models to the Kaplan-Meier curves from the IPW data from the NAVIGATOR study (March 2020 DC) (51). The OS for ECM was generated by fitting parametric models to the Kaplan-Meier curves from the IPW data from the BLU-285-1002 (5). Tested parametric models included: Exponential, Weibull, Gompertz, Log-normal and Log-logistic.

The selection of base case parametric functions for OS and PFS for avapritinib and ECM were informed by: Goodness-of-fit statistics (i.e., Akaike information criterion [AIC] and Bayesian information criterion [BIC]) and visual inspection to assess the concordance between predicted and observed PFS and OS curves. Finally clinical plausibility of long-term extrapolations was evaluated based on smoothed hazard plots and clinical plausibility. To keep the mortality risk of eligible patients, equivalent to or greater than the general population in all model cycles, all outcomes (OS, PFS) were capped by general mortality using Danish life tables provided by the DMC (70).

The study by Cassier et al. 2012 included a patient population that was similar to the patient population in the NAVIGATOR study (3). However, Cassier et al. does not provide patient characteristics for the unresectable or metastatic PDGFRA D842V mutation population, meaning there is no basis to suggest similarity of (or adjust for) baseline patient characteristics. For this reason, the best source for the comparison to avapritinib in the NAVIGATOR study is the IPW comparison to BLU-285-1002. In order to explore the uncertainty, the Cassier et al. study was used to present a naïve comparison to the NAVIGATOR study in a scenario analysis. Refer to Appendix D for further details on extrapolation and Appendix C.1.5 for details on the comparison with Cassier et al.

8.1.1.1 Extrapolation of overall survival (OS)

Table 25 summarises assumptions and extrapolation methods of OS.

Table 25 Summary of assumptions associated with extrapolation of overall survival (OS)

Method/approach	Description/assumption
Data input	Avapritinib: IPW data censoring for discontinuation - from the NAVIGATOR study (March 2020 DC) (51) (5) ECM: IPW data from BLU-285-1002 (4, 5)
Model	Five parametric distributions were fitted to the data. Single fitting for avapritinib and ECM arm (Exponential, Weibull, Gompertz, Log-normal, Log-logistic)
Assumption of proportional hazards between intervention and comparator	No assumption of proportional hazards
Function with best AIC fit	Avapritinib: Exponential, ECM: Weibull
Function with best BIC fit	Avapritinib: Exponential, ECM: Weibull
Function with best visual fit	Avapritinib: Exponential, ECM: Weibull
Function with the best fit according to external evidence	Not applicable
Function with best fit according to evaluation of smoothed hazard assumptions	Avapritinib: Log-logistic, EMC: Lognormal
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	Yes. The model incorporates a gradual transition of the OS hazard from the avapritinib arm to the ECM arm upon discontinuation from avapritinib treatment. In base case, the gradual loss of treatment effect upon discontinuation of avapritinib over 12 months has been assumed (38). This was in accordance with Danish market research and supported by a German clinical expert (38, 71). See Appendix D.1.8 for further details.
Assumptions of cure point	No
Selected parametric function in base case analysis	Avapritinib: Log-normal, ECM: Weibull
Validation of selected extrapolated curves	Clinical experts' opinions on clinical plausibility (52).

Abbreviations: IPW: inverse probability weighting, ECM: established clinical management, AIC akaike information criterion, BIC: bayesian information criterion, OS: overall survival.

Figure 11 and Figure 12 present the extrapolation models for OS in the avapritinib arm and the ECM arm, respectively. The figures show the extrapolation over 40 years (lifetime horizon). Refer to Appendix D.1.4 for further details.

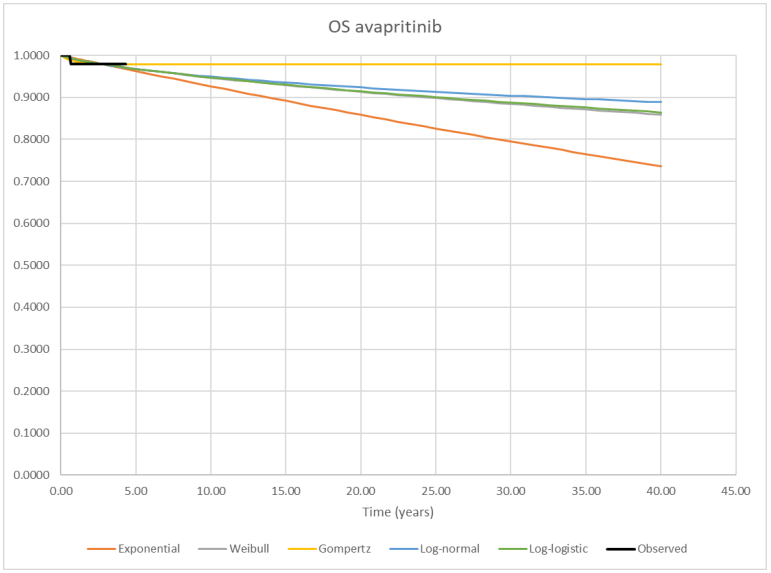

Figure 11 Extrapolation model for overall survival (OS), avapritinib, IPW adjusted (censored for discontinuation) data from NAVIGATOR - 40 years (480 months)

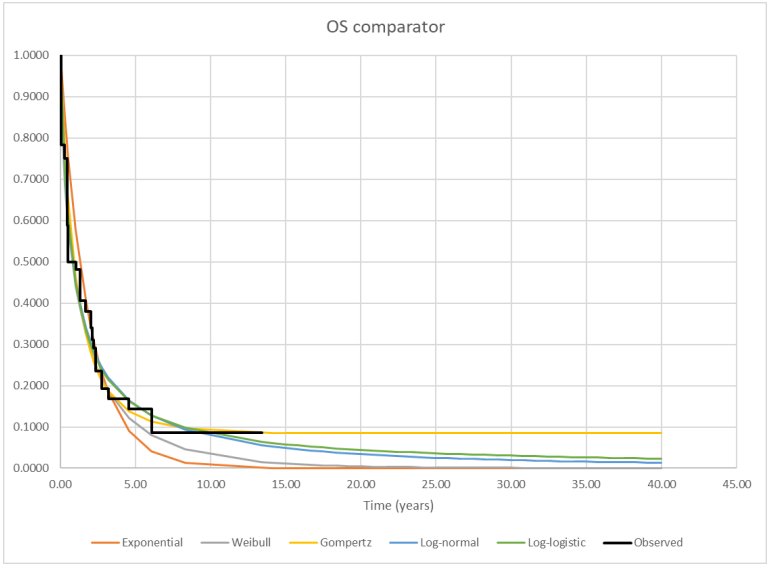

Figure 12 Extrapolation model for overall survival (OS), ECM, IPW adjusted time-to-event data from BLU-285-1002 - 40 years (480 months)

8.1.1.2 Extrapolation of progression-free survival (PFS)

The PFS for avapritinib was generated by fitting parametric models to the Kaplan-Meier curves from the IPW data from the NAVIGATOR study (March 2020 DC) (51). The PFS for ECM was generated by fitting parametric models to the Kaplan-Meier curves from the IPW data from the BLU-285-1002 (5). Parametric models included: Exponential, Weibull, Gompertz, Log-normal and Log-logistic. Table 26 summarises assumptions and extrapolation methods of PFS.

Table 26 Summary of assumptions associated with extrapolation of progression-free survival (PFS)

Method/approach	Description/assumption
Data input	Avapritinib: IPW data from the NAVIGATOR study (March 2020 DC)(51) (5) ECM: IPW data from BLU-285-1002 (4, 5)
Model	Five parametric distributions were fitted to the data. Single fitting for avapritinib and ECM arm (Exponential, Weibull, Gompertz, Log-normal, Log-logistic)
Assumption of proportional hazards between intervention and comparator	No assumption of proportional hazards
Function with best AIC fit	Avapritinib: Weibull, ECM: Weibull
Function with best BIC fit	Avapritinib: Weibull, ECM: Weibull
Function with best visual fit	Avapritinib: Weibull (and Exponential), ECM: Weibull
Function with the best fit according to external evidence	Not applicable
Function with best fit according to evaluation of smoothed hazard assumptions	Avapritinib: Lognormal, EMC: Gompertz
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No
Selected parametric function in base case analysis	Avapritinib: Weibull, ECM: Weibull
Validation of selected extrapolated curves	Clinical experts' opinions on clinical plausibility (52)

Abbreviations: IPW: inverse probability weighting, ECM: established clinical management, AIC akaike information criterion, BIC: bayesian information criterion.

Figure 13 and Figure 14 present the extrapolation models for PFS in the avapritinib arm and the ECM arm, respectively. The figures show the extrapolation over 40 years (lifetime horizon).

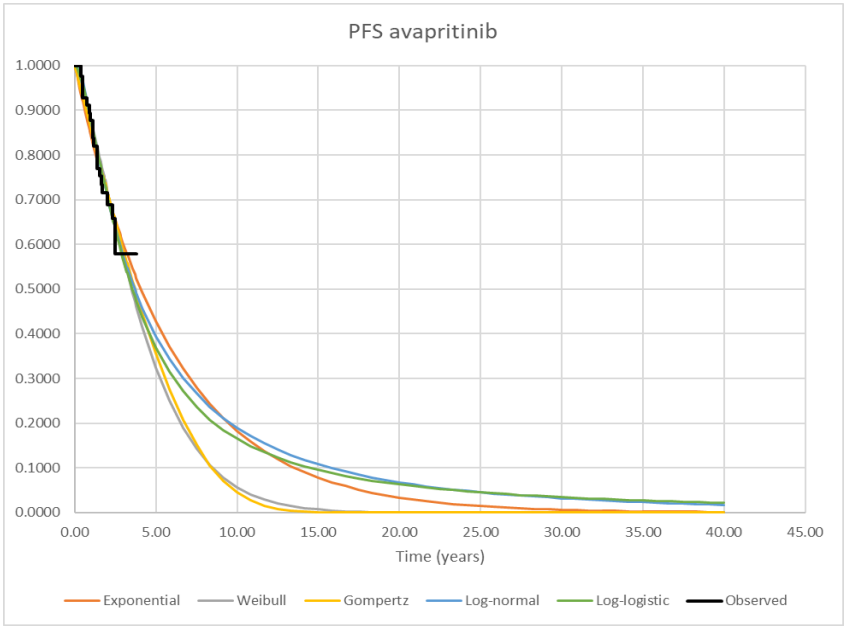

Figure 13 Extrapolation model for progression-free survival (PFS), avapritinib, IPW adjusted (censored for death) data from NAVIGATOR - 40 years (480 months)

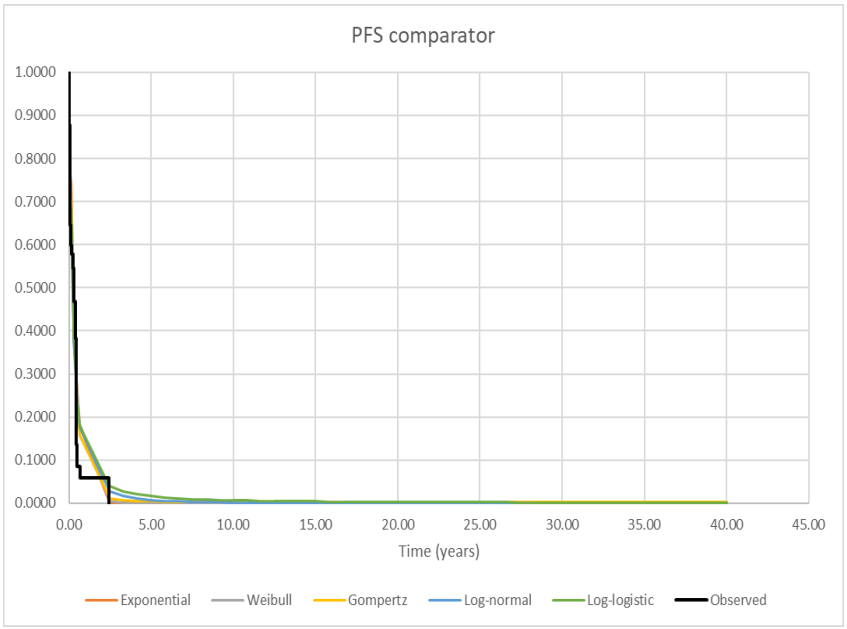

Figure 14 Extrapolation model for progression-free survival (PFS) 1L, ECM, IPW adjusted time-to-event data from BLU-285-1002 - 40 years (480 months)

Refer to Appendix D.2 for further details.

8.1.1.3 Extrapolation of time on treatment (ToT)

ToT for avapritinib was generated by fitting parametric models to the Kaplan-Meier curves from the IPW data from the NAVIGATOR study (January 2021 & March 2020 DC) (51). No ToT data was captured from BLU-285-1002 and therefore ToT was set equal to the PFS

generated for the ECM arm. Parametric models included: Exponential, Weibull, Gompertz, Log-normal and Log-logistic. Table 27 summarises assumptions and extrapolation methods of ToT.

Table 27 Summary of assumptions associated with extrapolation of time on treatment (ToT)

Method/approach	Description/assumption
Data input	Avapritinib: IPW data from the NAVIGATOR study (March 2020 DC) (51) (5) ECM: No data on ToT
Model	Five parametric distributions were fitted to the data. Single fitting for avapritinib arm (Exponential, Weibull, Gompertz, Log-normal, Log-logistic)
Assumption of proportional hazards between intervention and comparator	Not applicable
Function with best AIC fit	Avapritinib: Exponential, ECM: Not applicable
Function with best BIC fit	Avapritinib: Exponential, ECM: Not applicable
Function with best visual fit	Avapritinib: Exponential, ECM: Not applicable
Function with the best fit according to external evidence	Not applicable
Function with best fit according to evaluation of smoothed hazard assumptions	Not applicable
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	Yes. Linked to OS: The model link ToT to OS by using a "tunnel state" approach lasting for 12 cycles, the model calculates per-cycle probability of death based on time since discontinuation, capturing the gradual loss of avapritinib treatment effect on OS.
Assumptions of cure point	No
Selected parametric function in base case analysis	Avapritinib: Gompertz, ECM: Not applicable (equal to ECM PFS)
Validation of selected extrapolated curves	Clinical experts' opinions on clinical plausibility (52).

Abbreviations: IPW: inverse probability weighting, ECM: established clinical management, AIC akaike information criterion, BIC: bayesian information criterion, ToT: time on treatment, OS: overall survival, PFS: progression-free survival.

Figure 15 presents the extrapolation models for ToT in the avapritinib arm. The figure shows the extrapolation over 40 years (lifetime horizon). No data on ToT for the ECM is available.

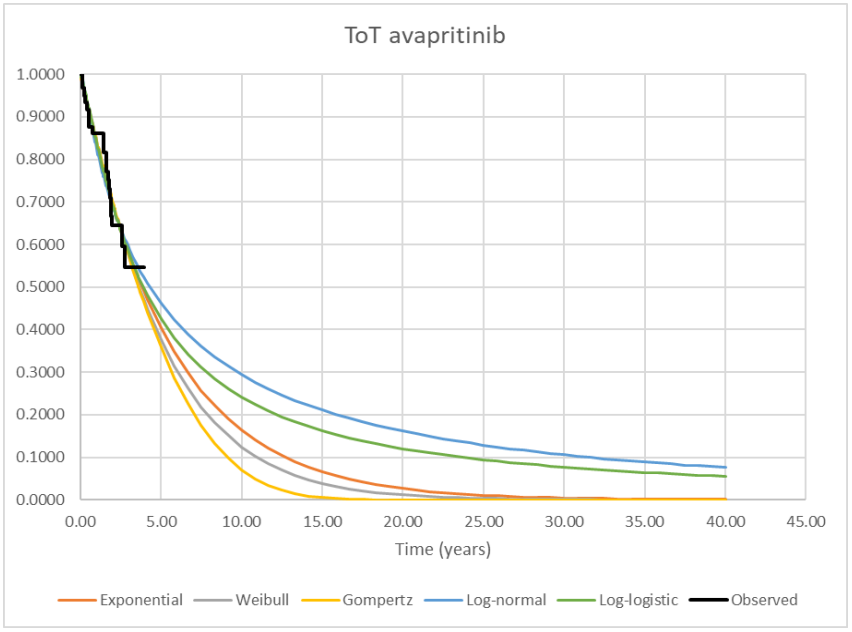

Figure 15 Extrapolation model for time on treatment (ToT), avapritinib, IPW adjusted (censored for death) data from NAVIGATOR - 40 years (480 months)

8.1.2 Calculation of transition probabilities

Table 28 Transitions in the health economic model (avapritinib arm)

Health state (from)	Health state (to)	Description of method	Reference
Avapritinib	Avapritinib	1-(sum of exit transitions)	(5)
	SOC1	Dynamic IPW PFS NAVIGATOR	(5)
	Death	Dynamic IPW OS NAVIGATOR censored for discontinuation (with 12 months tunnel state and linear interpolation to IPW OS BLU-285-1002)	(5)
SOC1	SOC1	1-(sum of exit transitions)	(5)
	SOC2	Dynamic IPW PFS2 BLU-285-1002	(5)
	Death	Dynamic IPW OS NAVIGATOR censored for discontinuation (with 12 months tunnel state and linear interpolation to IPW OS BLU-285-1002)	(5)
SOC2	SOC2	1-(sum of exit transitions)	(5)
	PD	Dynamic IPW PFS3 BL-285-1002	(5)
	Death	Dynamic IPW OS NAVIGATOR censored for discontinuation (with 12 months tunnel state and linear interpolation to IPW OS BLU-285-1002)	(5)
PD	PD	1-(sum of exit transitions)	(5)

Health state (from)	Health state (to)	Description of method	Reference
	Death	Dynamic IPW OS NAVIGATOR censored for discontinuation (with 12 months tunnel state and linear interpolation to IPW OS BLU-285-1002)	(5)
Death	Death	100%	(5)

Table 29 Transitions in the health economic model (ECM arm)

Health state (from)	Health state (to)	Description of method	Reference
ECM	ECM	1-(sum of exit transitions)	(5)
	SOC1	Dynamic IPW PFS1 BLU-285-1002	(5)
	Death	Dynamic IPW OS BLU-285-1002	(5)
SOC1	SOC1	1-(sum of exit transitions)	(5)
	SOC2	Dynamic IPW PFS2 BLU-285-1002	(5)
	Death	Dynamic IPW OS BLU-285-1002	(5)
SOC2	SOC2	1-(sum of exit transitions)	(5)
	PD	Dynamic IPW PFS3 BLU-285-1002	(5)
	Death	Dynamic IPW OS BLU-285-1002	(5)
PD	PD	1-(sum of exit transitions)	(5)
	Death	Dynamic IPW OS BLU-285-1002	(5)
Death	Death	100%	(5)

Transition probabilities are time varying and are based on the gradient of the IPW extrapolated data of NAVIGATOR (for avapritinib) and the BLU-285-1002 (for ECM) data (5). Each cycle, transition probability TP = Pr(prog) + Pr(death). $Pr(prog)_{SoC1,t}$ and $Pr(prog)_{SoC2,t}$ is the same in both arms every cycle and come from ECM SoC1 and SoC2 PFS censoring for death (where SoC1: standard of care 1, SoC2: standard of care 2, t: model cycle). $Pr(death)_{ECM,t}$ and $Pr(death)_{avapritinib,t}$ is different, and are based on ECM and avapritinib arm data, respectively. In each model cycle, pr(prog) is applied with a multiplier (relative risk ratio) of 1, so that progression rate is identical in both arms.

Figure 16 Proportion of patients in each health state receiving avapritinib (lifetime horizon)

Figure 17 Proportion of patients in each health state receiving ECM (lifetime horizon)

For practicalities in the model, the terminology of the model states AVA/1L, SoC1, SoC2, and PD corresponds to the following lines presented in results here in the model: PF1L, PF2L, PF3L, and PD.

8.2 Presentation of efficacy data from [additional documentation]

Not applicable.

8.3 Modelling effects of subsequent treatments

Subsequent treatment

Clinical data describing disease progression for patients with unresectable or metastatic U/M PGDFRA D842V mutated GIST after initial treatment with avapritinib is limited. The

NAVIGATOR study did not capture disease progression beyond the first line (51). As a result, there is no robust evidence to suggest that avapritinib impacts disease progression in later lines or stages. In our model, we assume equal probabilities of progression in the standard of care (SoC1 and SoC2) states between avapritinib and ECM arms. This approach allows us to capture the value of avapritinib in terms of improved progression-free survival and overall survival. However, this can be adjusted in the economic model by changing the PFS multiplier in the "Settings" sheet. The above-mentioned approach implies the following:

- PFS for ECM arm at first line, SoC1, and SoC2 must be censored for death.
- The per-cycle probability of progression and death can be separated.
- At each cycle, the probability of only progression at SoC1 and SoC2 (ECM) is combined with the avapritinib mortality rate (avapritinib OS data). Hence the probability of progression will be constant across arms and probability of death to be linked to the OS data.

We also make assumptions about the health state utility and resource use for patients with unresectable or metastatic U/M PGDFRA D842V mutated GIST. The model results show that avapritinib arm patients spend a higher proportion of time in earlier disease states compared to ECM arm patients, reflecting the extended PFS and OS seen in clinical evidence (52) . Figure 18 illustrates this structural assumption outlined above.

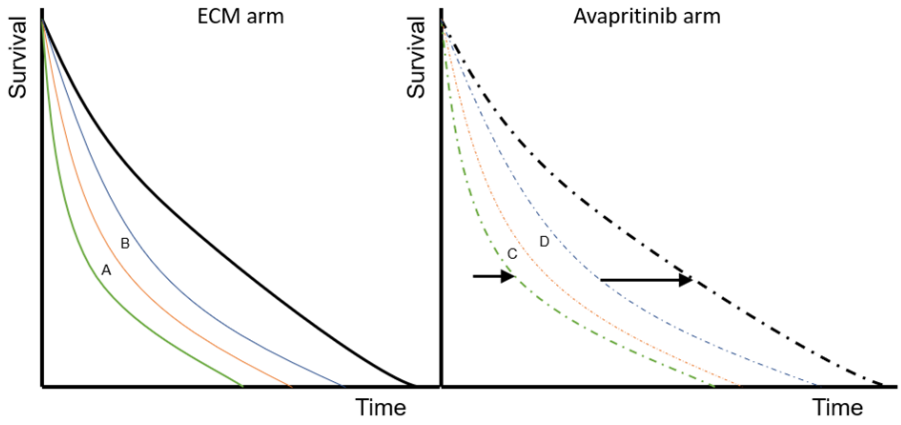

Figure 18 Example of structural assumption – equal rates of subsequent progression across treatment arms.

Abbreviations: ECM = established clinical management, IPW = inverse-probability weighting; SoC = standard of care.
Notes: A = expected time in the SoC1 health state in the ECM arm. B = expected time in the SoC2 health state in the ECM arm. C = expected time in the SoC1 health state in the avapritinib arm. D = expected time in the SoC2 health state in the avapritinib arm.

2L and 3L treatment

In the SoC1 and SoC2 health states, the PFS data for patients are obtained from BLU-285-1002 (5). The PFS analysis considers death events as censored, focusing solely on the risk of disease progression. As mentioned earlier, the base case assumption is that the rate of progression to the next treatment line remains the same for patients after avapritinib

treatment. This assumption is applied uniformly per model cycle (Figure 18). However, in order to explore the uncertainty regarding progression rate upon avapritinib discontinuation, a scenario analysis will investigate a slower progression rate. This assumption was supported by Danish market research (38).

Since the model is a Markov model, it must be ensured that patients transition to the right point in the progression curve in the model, which is not accounted for in the original model. To solve this issue, it was considered that setting the parametric distribution for PFS with 2L and 3L comparator to Exponential. It assumes that the likelihood of an event occurring remains constant over time, regardless of where a patient is on the progression curve (in reality, the hazard rate may not be constant, and treatment effects may change over time, however, it was considered simpler and more feasible compared with e.g. introducing tunnel-states to account for time-varying transition probabilities.

8.4 Other assumptions regarding efficacy in the model

Discontinuation censoring

The OS analysis from NAVIGATOR used censors for discontinuation events, hence only capturing mortality for those patients still receiving avapritinib. This choice was made because simply using the full IPW OS data from the NAVIGATOR study breaks any connection between ToT and treatment effect. A simple extrapolation of the full OS is insufficient due to the short follow-up period and incomplete ToT data. Therefore, a more appropriate approach is needed, explicitly linking ToT to OS and allowing for a gradual loss of treatment effect.

Mortality rates for on-treatment patients were obtained from OS data in NAVIGATOR (51), accounting for discontinuation, while off-treatment patients were modelled using OS data from ECM (5). The rate of progression was derived from death-censored PFS in the ECM data and applied to post-avapritinib patients. For this reason, mortality is only applied to those patients remaining on avapritinib, or those who are still benefiting from avapritinib beyond discontinuation as described in Appendix D.1.8. The model has the flexibility to change the method of OS extrapolation in the “Settings” sheet in the model by selecting direct OS extrapolation.

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

Table 30 presents the estimates in the model for the modelled average OS and PFS (first line). The estimates are undiscounted, without half-cycle correction and adjusted for background mortality of the Danish population, as requested by the DMC. For practicalities, the terminology of the model states AVA/1L, SoC1, SoC2, and PD corresponds to the following lines in the model: PF1L, PF2L, PF3L, and PD.

Table 30 Expected time in each living state in the cost-effectiveness model—base case, undiscounted and without half-cycle correction.

	Modelled average overall survival	Modelled average progression-free survival				Observed median (OS) from relevant study
		PF 1L	PF 2L (SoC1)	PF 3L (SoC2)	PD	
Avapritinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ECM: established clinical management, PF: progression-free, PD: progressed disease, SoC: standard of care.

Note: [1]After 25.5 months more than half of the patients were still living. Thus, the median OSS was not reached in the IPW NAVIGATOR analysis (base case).

Table 31 presents the modelled average treatment length and time in the model health states. With median survival in the IPW NAVIGATOR analysis not reached after 26 months (13 months beyond the median survival in the IPW BLU-285-1002 analysis), the clinical evidence clearly supports the notion of avapritinib being a disease-modifying, life-extending therapy.

Table 31 Overview of modelled average treatment length (months) and time in model health state (years), undiscounted and not adjusted for half cycle correction

Treatment	Treatment length [months]	PF 1L	PF 2L (SoC1)	PF 3L (SoC2)	PD
Avapritinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviation: ECM: established clinical management, PF: progression-free, PD: progressed disease, SoC: standard of care.

9. Safety

9.1 Safety data from the clinical documentation

The latest available data on the safety of avapritinib for GIST patients is available from the January 2021 DC of the NAVIGATOR study with a median follow-up of 27.5 months for the safety population (51).

The safety population consists of all patients from the NAVIGATOR study who received at least one dose of avapritinib (51). The safety population included 250 patients from both parts 1 and 2 of the NAVIGATOR study, of which, 56 patients (20 patients from part 1 and 36 patients from part 2) harboured the PDGFRA D842V mutation (51). We added data for patients without the PDGFRA D842V mutation, as there no clinical evidence to suggest that AEs would occur more frequently in patients with or without the PDGFRA D842V mutation or regardless of treatment line; therefore, given the ultra-orphan nature of the

condition, it was considered more appropriate to include evidence for the maximum number of patients to provide a clear safety profile for avapritinib (51). This approach aligns with the safety data that were presented to the EMA for the SmPC. In addition, safety data for the primary efficacy population of PDGFRA D842V patients receiving 300 mg/400 mg of avapritinib (N=38) as well the PDGFRA D842V patients who received all doses of avapritinib (N=56) is also provide below to provide better context on the adverse event profile for this population.

The safety population were treated for a median duration of 28.6 weeks, with a median average daily dose of 288 mg in the 300 mg starting dose group and 339 mg in the 400 mg starting dose group (51). The 300 mg/400 mg PDGFRA D842V population were treated for a median duration of 110.6 weeks, with a median average daily dose of 210.5 mg (51). PDGFRA D842V patients who received all doses of avapritinib were treated for a median duration of 113.3 weeks, with a median average daily dose of 203.0 mg (51).

Table 32 Overview of safety events for avapritinib; NAVIGATOR; safety population analysis set & PDGFRA D842V 300 mg/400 mg; PDGFRA D842V all doses; January 2021 DC

	Avapritinib (N=250)	Avapritinib 300mg /400mg (N = 38)	Avapritinib All doses (N = 56)
Number of adverse events, n	249	38	53
Number and proportion of patients with ≥1 adverse events, n (%)	249 (99.6)	38 (100)	53 (94.6)
Number of serious adverse events, n	165	30	47
Number and proportion of patients with ≥ 1 serious adverse events, n (%)	165 (66.0)	30 (78.9)	47 (83.9)
Number of CTCAE grade ≥ 3 events, n	199	36	53
Number and proportion of patients with ≥ 1 CTCAE grade 3 events, n (%)	199 (79.6)	36 (94.7)	53 (94.6)
Number of adverse reactions, n	NR	NR	NR
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	NR	NR	NR
Number and proportion of patients who had a dose reduction, n (%)	137 (54.8)	NR	NR
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	250 (100)	38 (100)	56 (100)

	Avapritinib (N=250)	Avapritinib 300mg /400mg (N = 38)	Avapritinib All doses (N = 56)
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	69 (27.6)	NR	NR

Abbreviations: NR = not reported

Note: Adverse Events are coded using MedDRA 18.1. All treatment emergent adverse events including treatment emergent serious adverse events are included in summary statistics. If a patient has multiple events of the same severity, relationship or outcome, then they are counted only once in that severity, relationship or outcome. However, patients can be counted more than once overall.

Source: NAVIGATOR CSR; Table 14.3.1.1, Table 99.3.4.1, Table 99.3.3.1 (51)

Serious adverse events with a frequency of ≥5% is provided in Table 33 below. Full details of serious adverse events and adverse events of special interest from the NAVIGATOR study are provided in Appendix E.

Table 33 Serious adverse events with a frequency of ≥5% for avapritinib; NAVIGATOR; safety population analysis set & PDGFRA D842V 300 mg/400 mg; PDGFRA D842V all doses; January 2021 DC

Adverse events	Avapritinib (N=250)	Avapritinib 300mg /400mg (N = 38)	Avapritinib All doses (N = 56)
Adverse event, n (%)	165 (66.0)	30 (78.9)	47 (83.9)
Anaemia	27 (10.8)	6 (15.8)	7 (12.5)
Disease progression	20 (8.0)	3 (7.9)	4 (7.1)
Gastroenteritis	3 (1.2)	2 (5.3)	3 (5.4)
Gastrointestinal haemorrhage	6 (2.4)	1 (2.6)	3 (5.4)
Pleural effusion	6 (2.4)	2 (5.3)	3 (5.4)
Colitis	2 (<1)	2 (5.3)	2 (3.6)
Gastric haemorrhage	2 (<1)	2 (5.3)	2 (3.6)
Melaena	3 (1.2)	2 (5.3)	2 (3.6)
Pneumonia	7 (2.8)	2 (5.3)	2 (3.6)
Pneumonia aspiration	2 (<1)	2 (5.3)	2 (3.6)
Upper respiratory tract infection	2 (<1)	2 (5.3)	2 (3.6)
Urinary tract infection	3 (1.2)	2 (5.3)	2 (3.6)
Deaths	35 (14.0)	-	-

Note: Adverse Events are coded using MedDRA 18.1. AEs refer to TEAEs which is defined as an AE that occurs during or after administration of the first dose of study drug through 30 days after the last dose of study drug, any event that is considered study drug-related regardless of the start date of the event, or any event that is present at baseline but worsens intensity or is subsequently considered study drug-related by the Investigator. All TEAEs including treatment emergent serious adverse events are included in summary statistics. If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count.

Source: NAVIGATOR CSR; Table 14.3.3.1; Table 14.3.3.3 (51)

Safety data is used in the health economic model

Due to the sparsity of available data, ITC for safety outcomes could not be conducted. In the absence of evidence regarding the AEs experienced by patients undergoing ECM in GIST harbouring the PDGFRA D842V mutation, evidence from the pivotal clinical trials for these ECM treatments was used for comparison with the NAVIGATOR study. The AE outcomes and frequencies for the ECM for the base case are derived from Demetri et al. on imatinib (63) (64) (65). The justification for the selection of imatinib safety data are described in section 9.2.

Only grade 3-4 AEs with incidence of greater than 5% were considered in the health economic analysis. For the base case, the safety population – PDGFRA D842V, all doses, (N = 56) was used. The number of occurrences and the number of patients experiencing the AE are included on the sheet "Adverse Events" for each treatment arm. Table 34 presents the frequency of AE used in the health economic model. In a scenario analysis, the impact of changing the safety data to the full population will be explored.

Table 34 Adverse events used in the health economic model

Adverse events	Avapritinib	ECM (imatinib)		
	Frequency used in economic model for intervention	**Frequency used in economic model for ECM**	**Source**	**Justification**
Follow-up, months	30.0	9.5	NAVIGATOR (51)/Demetri et al (63)	NA
Adverse event, n (%)	53 (92.9))	147	NAVIGATOR (51)/Demetri et al (63)	Grade ≥3 AEs with ≥ 5% incidence in the full safety population*
Anaemia	24 (42.9)	3 (2)	–	–
Decreased appetite	3 (5.3)	NA	–	–
Diarrhoea	5 (8.9)	3 (2)	–	–
Dyspnoea	3 (5.4)	NA	–	–
Fatigue	20 (10.0)	NA	–	–
Oedema	NA	2 (1.4)	–	–
Haemorrhage	6 (3.0)	7 (4.8)	–	–
Hypertension	3 (5.4)	NA	–	–
Hypokalaemia	4 (7.1)	NA	–	–

Adverse events	Avapritinib	ECM (imatinib)		
Neutropenia	5 (8.9)	7 (4.8)	–	–
Neutrophil count decreased	6 (10.7)	NA	–	–
Pleural effusion	4 (7.1)	NA	–	–
Hypocalcaemia	4 (7.1)	NA	–	–
Clostridium difficile infection	3 (5.4)	NA	–	–
Disease progression	3 (5.4)	NA	–	–

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

The selection of AE outcomes for the ECM arm is based on external literature. The ECM arm consists of three different treatment lines (imatinib, sunitinib and regorafenib), each with different safety profiles. The AE outcomes and their frequencies for the ECM arm are derived from three studies by Demetri et al. on imatinib, sunitinib, and regorafenib (63) (64) (65). However, since the base case is assuming 20% of patients in the ECM arm will receive imatinib, and 0% will receive sunitinib and regorafenib, the AE outcomes and their frequencies for the ECM arm are derived from the study on imatinib. For this reason, AE outcomes and frequencies from sunitinib and regorafenib will only be applied in the scenario analysis exploring a 100% use of TKIs.

Demetri et al 2002 reported AEs associated with imatinib treatment (63). The study reported Grade 3–4 events that occurred in ≥5% of patients.

Table 35 presents the included AEs for the ECM arm in the model. In the table the frequency of used in the economic model is considered as per cycle probability.

Table 35 Adverse events that appear in more than 5 % of patients

Adverse events	ECM, imatinib (N=147) (63)		ECM, sunitinib (N=202) (64)		ECM, regorafenib (N=132) (65)		Difference, % (95 % CI)	
	Number of adverse events	Frequency used in economic model for comparator	Number of adverse events	Frequency used in economic model for comparator	Number of adverse events	Frequency used in economic model for comparator	Number of adverse events	Frequency used in economic model for comparator
Adverse event, n	147	NA	202	NA	132	NA	NA	NA
Diarrhoea	3 (below 5%, not included)	0.00216	7 (below 5%, not included)	0.00266	7 (5.3)	0.01142	NA	NA
Dermatitis/Rash	4 (below 5%, not included)	0.00288	NA	0.00000	29 (22.0)	0.04729	NA	NA
Fatigue	NA	0.00000	10 (5.0)	0.00380	3 (below 5%, not included)	0.00489	NA	NA
Hypertension	NA	0.00000	6 (below 5%, not included)	0.00228	30 (22.7)	0.04892	NA	NA
Lymphopenia	NA	0.00000	19 (9.4)	0.00721	NA	0.00000	NA	NA
Neutropenia	7 (below 5%, not included)	0.00503	20 (9.9)	0.00759	NA	0.00000	NA	NA

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

Since HRQoL data was not collected in the NAVIGATOR study or BLU-285-1002, the health state utility values used in the model base case were taken from the VOYAGER trial (6) and from previous GIST NICE TAs, TA86/TA209 (TA209, final appraisal determination papers, point 4.2.13, page 16 of 45) and TA179 (final appraisal determination papers, point 3.10, page 7 of 26) (56-58). The AE disutilities were sourced from a targeted review of the literature or from previous appraisals (please see Appendix I. for additional details). Table 36 summarizes the included HRQoL instruments.

Table 36 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
ECOG performance	TA86/TA209 (imatinib)(56, 57)	The avapritinib/1L utility value are based on TA86/TA209 (TA209, final appraisal determination papers, point 4.2.13, page 16 of 45). ECOG performance mapped to EQ-5D values by clinical experts. In this submission, assumed to have been calculated with UK tariffs.
EQ-5D	TA179 (sunitinib)(58)	SoC1 utility value is based on TA179 (final appraisal determination papers, point 3.10, page 7 of 26). In this submission, assumed to have been calculated with UK tariffs.
EQ-5D-5L	VOYAGER trial (6)	SoC2 and PD health states utility values are based on the VOYAGER trial. Estimate is based on mean of both trial arms. In this submission, assumed to have been calculated with UK tariffs.

Abbreviations: ECOG: Eastern Cooperative Oncology Group, TA: technology appraisal, EQ-5D: EuroQol-5 dimension, SoC: standard of care, PD: progressed disease.

10.1 Presentation of the health-related quality of life

This section is not applicable as the health state utilities included in the model are sourced from other studies besides those informing the clinical effectiveness.

10.1.1 Study design and measuring instrument

Not applicable.

10.1.2 Data collection

Not applicable.

10.1.3 HRQoL results

Not applicable.

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

The systematic review did not identify any relevant HRQoL studies assessing patients with unresectable or metastatic PDGFRA D842V-mutated GIST (please see Appendix I). Health state utilities used in the model are obtained from the VOYAGER study (6) and previous NICE appraisals. It is recognised that the VOYAGER data reflect the most recent evidence. However, utility values derived from the ITT population are only applicable to SoC2 and progressive disease health states due to the limited inclusion criteria. For the HSUV applicable in the first line and SoC1 health states, utilities derived from TA86/TA209 (TA209, final appraisal determination papers, point 4.2.13, page 16 of 45) and TA179 (final appraisal determination papers, point 3.10, page 7 of 26) have been used (56-58).

The AE disutilities were sourced from a targeted review of the literature of previous appraisals (refer to Table 39). See section 10.3.3 for the presentation of the HSUVs measured in VOYAGER trial.

10.2.1 HSUV calculation

Since no IPD from the TA86/TA209/TA179 was available, it was not possible to apply Danish preference weights to the first line and SoC1 HSUV. To ensure consistency with all HSUV and avoid selective adjustment, the utilities (SoC2 and PD) derived from the VOYAGER study (60) are not mapped to Danish EQ-5D-5L tariffs in the base case analysis. A scenario analysis was conducted to assess the impact of applying Danish weights to the two HSUV derived from the EQ-5D-5L instrument used in the VOYAGER trial.

The health states utility values were adjusted to ensure that the HRQoL of the patient cohort at any given age does not exceed the HRQoL of the general Danish background population. The utilities were age-adjusted using a general population multiplier derived from Danish age-specific data sourced from DMC's guidelines (53).

10.2.1.1 Mapping

<u>HSUV – first line and SoC1</u>

HSUVs were informed by previous NICE appraisals. In TA86/TA209 for imatinib (56, 57), 3 clinicians answered a questionnaire to map patients' ECOG performance from the B222 trial to EQ-5D (72). In TA179 for sunitinib (58), EQ-5D data were collected from patients receiving BSC in the A6181004 trial using an EQ-5D questionnaire (64). Utility values from the previous appraisals were derived using UK preference scores. No further information is available.

<u>HSUV – SoC2 and PD</u>

HSUVs for SoC2 and PD were informed by the VOYAGER study. In the VOYAGER study, HRQoL was collected as an exploratory endpoint using the EQ-5D-5L questionnaire. No mapping was applied.

10.2.2 Disutility calculation

Given the scarce evidence regarding the utility decrements applicable to the PDGFRA D842V mutated GIST population, and to maintain a conservative approach of the HSUVs accrued by patients receiving avapritinib, no utility decrements were applied in the base case. However, to align with the analysis submitted to NICE (TA730, committee papers, Table 49), utility decrements associated with adverse events (AEs) of grade 3-4 and based on published articles and previous NICE appraisals were included in a scenario analysis (refer to Table 39). AEs of grade 1-2 were assumed to have no disutility. The mean duration of adverse events in the model is seven days, informed by the previous NICE appraisal, TA730 (TA730, committee papers, section 4.2.7.4, original source: TA176 and TA240) (59) and by Freeman et al. (73) and confirmed with clinical experts as being a reasonable duration. An overview of the utility decrements applied in a scenario analysis is presented in Table 39.

10.2.3 HSUV results

Table 37 presents an overview of health state utility values used in the model in the base case. Additionally, three scenario analyses were conducted, which are presented below in sections 10.2.3.1 to 0.

Table 37 Overview of health state utility values applied as base case in the model

HSUVs	Results (SD)	Instrument	Tariff (value set) used	Comments
Ava/first-line	0.935 (0.094)	ECOG	UK	Mapping of patient's ECOG performance to EQ-5D by clinicians in the B222 study (72).
SoC1	0.781 (0.078)	EQ-5D	UK	Estimate is derived from the GIST patients receiving BSC in the A6181004 study (64).
SoC2	0.782 (0.078)	EQ-5D-5L	UK	Estimate is based on mean of both trial arms in third-line treatment in the VOYAGER trial (6).
PD	0.727 (0.073)	EQ-5D-5L	UK	Estimate is based on mean of both trial arms in fourth-line treatment in the VOYAGER trial (6).

Abbreviations: HSUV: health state utility value; SoC: standard of care; PD: progressed disease; EQ-5D-5L: EuroQol 5-Dimensional 5-Level; ECOG: Eastern Cooperative Oncology Group; GIST: gastrointestinal stromal tumour; BSC: best supportive care; AE: adverse event; NA: not applicable; TA: technology appraisal.

10.2.3.1 Scenario – first line

In avapritinib's recent GIST appraisal from NICE (TA730, committee papers, section 4.2.7.2)(59), the ERG considered the HSUV for the first line (AVA and ECM) of 0.935 implausibly high and instead suggested to use general utility for the same age group as patients in SoC1 health state. A similar approach was taken to conduct a scenario analysis

in the Danish context. According to a recent publication by Hvidberg et al. (2023), the Danish general population utility of this age group based on EQ-5D instrument is 0.832 (74). Therefore, a HSUV of 0.832 for first line of has been explored in a scenario analysis.

10.2.3.2 Scenario – alternative HSUV SoC2 and PD

As mentioned in section 10.2.1, scenario analysis was conducted to assess the impact of applying Danish weights to the VOYAGER data. The recalculation of the HSUV with Danish specific tariffs, based on the method described by Jensen et al, 2021 (75) resulted in the following HSUV (76), shown in Table 38.

Table 38 Danish weighted utilities applied in a scenario analysis in the economic model

HSUV	Result (95% CI)	Tariff
SoC2	0.8493 (0.83; 0.8696)	Danish tariff (60) (76)
PD	0.8065 (0.76; 0.857)	Danish tariff (60) (76)

Abbreviations: SoC: standard of care, PD: progressed disease, CI: confidence interval.

10.2.3.3 Scenario - AE utility decrements included in the economic model

As discussed in section 10.2.2, Table 39 below are reported the utility decrements included in a scenario analysis. The AE utility decrement included are sourced from NICE TA730 (TA730, committee papers, Table 49) (59).

Table 39 Utility decrements applied as a scenario analysis in the model

AE utility decrements	Results (SD)	Instrument	Tariff (value set) used	Comments
Abdominal pain	0.069	NA	NA	Doyle et al. (2008) (77) [TA176/TA240]
Abnormal liver function results	0.200	NA	NA	Assume the maximum of the available utility decrements
Anaemia	0.085	NA	NA	Harrow et al. (2011) (78) [TA176/TA240]
Ascites	0.200	NA	NA	Assume the maximum of the available utility decrements
Asthenia	0.115	NA	NA	Assume equal to disutility for fatigue
Blood bilirubin increased	0.200	NA	NA	Assume the maximum of the available utility decrements
Confusional state	0.200	NA	NA	Assume the maximum of the available utility decrements
Decreased appetite	0.158	NA	NA	Freeman et al. (2015) (73), assumed anorexia
Diarrhoea	0.103	NA	NA	Lloyd et al. (2006) (79) [TA176/TA240]

AE utility decrements	Results (SD)	Instrument	Tariff (value set) used	Comments
Dermatitis/rash	0.032	NA	NA	Nafees et al. (2008) (80) [TA176/TA240]
Dyspnoea	0.200	NA	NA	Assume the maximum of the available utility decrements
Fatigue	0.115	NA	NA	Lloyd et al. (2006) (79) [TA176/TA240]
Edema	0.060	NA	NA	Freeman et al. (2015) (73), Table 112
Hemorrhage	0.200	NA	NA	Assume the maximum of the available utility decrements
Hypertension	0.069	NA	NA	Doyle et al. (2008) (77) [TA176/TA240]
Hypokalaemia	0.115	NA	NA	Assume equal to disutility for fatigue
Hyponatraemia	0.090	NA	NA	Assume equal to disutility for neutropenia
Hypophosphataemia	0.090	NA	NA	Assume equal to disutility for neutropenia
Leukopenia	0.090	NA	NA	Assume equal to disutility for neutropenia
Lymphopenia	0.090	NA	NA	Assume equal to disutility for neutropenia
Nausea	0.048	NA	NA	Nafees et al. (2008)
Neutropenia	0.090	NA	NA	Nafees et al. (2008) (80) [TA176/TA240]
Neutrophil count decreased	0.090	NA	NA	Assume equal to disutility for neutropenia
Pleural effusion	0.200	NA	NA	Assume the maximum of the available utility decrements
Pneumonia	0.200	NA	NA	Freeman et al. (2015) (73), Table 110
Sepsis	0.195	NA	NA	Freeman et al. (2015) (73), Table 106
Vomiting	0.103	NA	NA	Lloyd et al. (2006) (79) [TA176/TA240]

Abbreviations: SD: standard deviation, NA: not applicable, TA: technology appraisal.

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

In the absence of HRQoL data collected in the NAVIGATOR study and BLU-285-1002, the HSUV used in the model were derived from the VOYAGER study (6) and from previous NICE appraisals (56-58).

10.3.1 Study design

HSUVs for SoC2 and PD were informed by the VOYAGER study. In alignment with the Danish reference case, the VOYAGER collected HRQoL data using the EQ-5D-5L questionnaire. As the population with the PDGFRA D842V mutation was a subgroup in the VOYAGER study, the groups were not randomized based on baseline third and fourth-line EQ-5D values. Because of this and the small sample size (7 for avapritinib and 6 for regorafenib), these numerical differences at baseline cannot reasonably be interpreted to be meaningful. Therefore, the HRQoL results are based on the ITT population in the VOYAGER study. The HRQoL data from the VOYAGER study is the most recently available data coming from a large sample of patients with unresectable or metastatic GIST (6).

10.3.2 Data collection

The EQ-5D data from VOYAGER indicates no meaningful differences between the avapritinib arm and regorafenib arm before initiation of treatment. Attrition bias impacted the utility analysis, as patients progressed and discontinued their participation, resulting in a sample that predominantly consisted of the healthiest patients. Therefore, a consideration of utility over time is likely to be unreliable and supports the use of baseline values for the cost-effectiveness analysis.

The pattern of missing data and completion from the VOYAGER EQ-5D data on the ITT population in 3rd (avapritinib: 207, regorafenib: 201) and 4th line (avapritinib: 33, regorafenib: 35) is demonstrated in Table 40 and Table 41.

The imputation rules were as follows:

- No imputation will be made for completely missing date unless otherwise specified.
- For missing data, if the stop date is not missing, and the imputed start date is after the stop date, the start date will be imputed by the stop date.
- For missing data, if the start date is not missing, and the imputed stop date is before the start date, then the imputed stop date will be equal to the start date.
- Any imputed dates need to be logical. For example, last dose date should not be later than death date.

Table 40 Pattern of missing data and completion, 3rd line (informing SoC2 in the model)

Time point	HRQoL population N (60)	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Avapritinib	207	9 (4,35%)	NA	NA
Regorafenib	201	14 (6,97%)	NA	NA
Avapritinib	207	29 (14,01%)	NA	NA
Regorafenib	201	24 (11,94%)	NA	NA
Avapritinib	207	49 (23,67%)	NA	NA
Regorafenib	201	38 (18,91%)	NA	NA
Avapritinib	207	93 (44,93%)	NA	NA
Regorafenib	201	87 (43,28%)	NA	NA
Avapritinib	207	91 (43,96%)	NA	NA
Regorafenib	201	74 (36,82%)	NA	NA
Avapritinib	207	204 (98,55%)	NA	NA
Regorafenib	201	200 (99,50%)	NA	NA
Avapritinib	207	139 (67,15%)	NA	NA
Regorafenib	201	114 (56,72%)	NA	NA

Time point	HRQoL population N (60)	Missing N (%)	Expected to complete N	Completion N (%)
Avapritinib	207	206 (99,52%)	NA	NA
Regorafenib	201	200 (99,50%)	NA	NA
Avapritinib	207	169 (81,64%)	NA	NA
Regorafenib	201	150 (74,63%)	NA	NA
Avapritinib	207	205 (99,03%)	NA	NA
Regorafenib	201	200 (99,50%)	NA	NA
Avapritinib	207	187 (99,03%)	NA	NA
Regorafenib	201	163 (99,50%)	NA	NA
Avapritinib	207	206 (90,34%)	NA	NA
Regorafenib	201	200 (81,09%)	NA	NA
Avapritinib	207	193 (99,52%)	NA	NA
Regorafenib	201	172 (99,50%)	NA	NA
Avapritinib	207	206 (93,24%)	NA	NA
Regorafenib	201	200 (85,57%)	NA	NA
Avapritinib	207	202 (99,52%)	NA	NA

Time point	HRQoL population N (60)	Missing N (%)	Expected to complete N	Completion N (%)
Regorafenib	201	190 (99,50%)	NA	NA
Avapritinib	207	206 (97,58%)	NA	NA
Regorafenib	201	201 (94,53%)	NA	NA
Avapritinib	207	204 (99,52%)	NA	NA
Regorafenib	201	193 (100,00%)	NA	NA
Avapritinib	207	207 (98,55%)	NA	NA
Regorafenib	201	199 (96,02%)	NA	NA
Avapritinib	207	207 (100,00%)	NA	NA
Regorafenib	201	201 (99,00%)	NA	NA

Table 41 Pattern of missing data and completion, 4th line (informing PD health state in the model)

Time point		HRQoL population N (60)	Missing N (%)	Expected to complete N	Completion N (%)
		Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	Avapritinib	33	3 (9,09%)	NA	NA
	Regorafenib	35	3 (8,57%)	NA	NA
Week 4	Avapritinib	33	4 (12,12%)	NA	NA

Time point		HRQoL population N (60)	Missing N (%)	Expected to complete N	Completion N (%)
	Regorafenib	35	2 (5,71%)	NA	NA
Week 8	Avapritinib	33	14 (42,42%)	NA	NA
	Regorafenib	35	5 (14,29%)	NA	NA
Week 12	Avapritinib	33	20 (60,61%)	NA	NA
	Regorafenib	35	12 (34,29%)	NA	NA
Week 16	Avapritinib	33	15 (45,45%)	NA	NA
	Regorafenib	35	13 (37,14%)	NA	NA
Week 20	Avapritinib	33	33 (100,00%)	NA	NA
	Regorafenib	35	35 (100,00%)	NA	NA
Week 24	Avapritinib	33	22 (66,67%)	NA	NA
	Regorafenib	35	18 (51,43%)	NA	NA
Week 28	Avapritinib	33	33 (100,00%)	NA	NA
	Regorafenib	35	35 (100,00%)	NA	NA
Week 32	Avapritinib	33	25 (75,76%)	NA	NA
	Regorafenib	35	22 (62,86)	NA	NA
Week 36	Avapritinib	33	33 (100,00%)	NA	NA
	Regorafenib	35	34 (97,14%)	NA	NA
Week 40	Avapritinib	33	26 (78,79%)	NA	NA
	Regorafenib	35	27 (77,14%)	NA	NA
Week 44	Avapritinib	33	33 (100,00%)	NA	NA
	Regorafenib	35	35 (100,00%)	NA	NA
Week 48	Avapritinib	33	26 (78,79%)	NA	NA
	Regorafenib	35	28 (80,00%)	NA	NA
Week 52	Avapritinib	33	33 (100,00%)	NA	NA
	Regorafenib	35	35 (100,00%)	NA	NA
Week 56	Avapritinib	33	32 (96,97%)	NA	NA
	Regorafenib	35	33 (94,29%)	NA	NA
Week 60	Avapritinib	33	33 (100,00%)	NA	NA
	Regorafenib	35	35 (100,00%)	NA	NA
Week 64	Avapritinib	33	33 (100,00%)	NA	NA
	Regorafenib	35	34 (97,14%)	NA	NA
	Avapritinib	33	33 (100,00%)	NA	NA

Time point		HRQoL population N (60)	Missing N (%)	Expected to complete N	Completion N (%)
Week 72	Regorafenib	35	34 (97,14%)	NA	NA
Week 80	Avapritinib	33	33 (100,00%)	NA	NA
	Regorafenib	35	34 (97,14%)	NA	NA

10.3.3 HRQoL Results

EQ-5D data for the overall ITT population from the VOYAGER study from baseline and up to week 80 were measured for patients treated at third and fourth line (6) (81). This data is presented in Table 42. Utility data used in the model is EQ-5D data at baseline. Figure 19 and Figure 20 display the mean change (including error bars showing the standard deviations) from baseline through 80 weeks for both avapritinib and regorafenib at third- and fourth line, respectively.

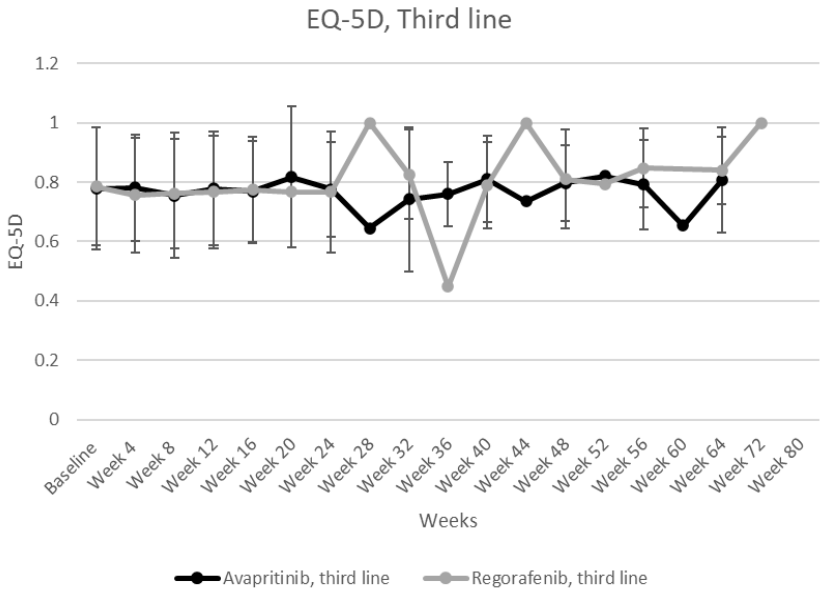

Figure 19 EQ-5D data from the VOAYGER, ITT-population - third line

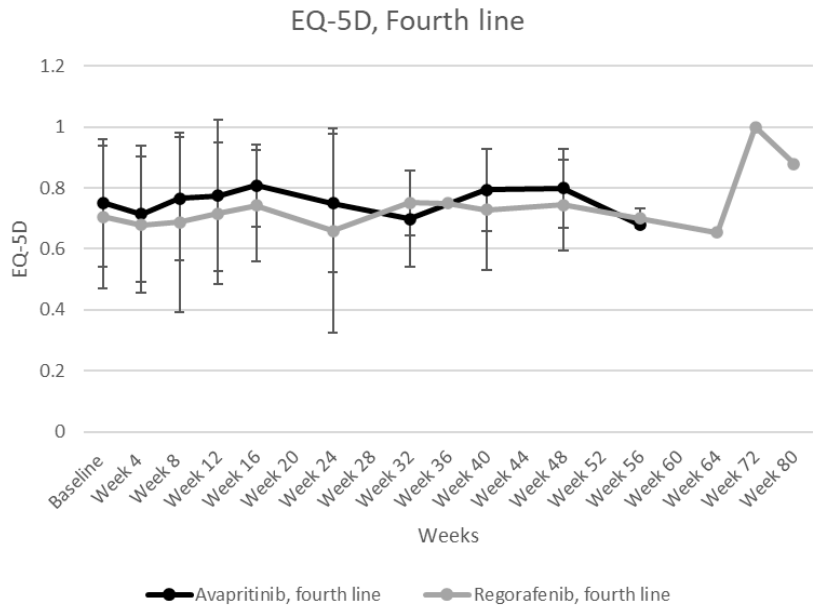

Figure 20 EQ-5D data from the VOYAGER, ITT population - fourth line

Table 42 HRQoL EQ-5D summary statistics

		Avapritinib (60)		Regorafenib (60)	
		N	Mean (SD)	N	Mean (SD)
Baseline	3rd line	198	0.779 (0.2065)	187	0.786 (0.1984)
	4th line	30	0.751 (0.2103)	32	0.705 (0.2330)
Week 4	3rd line	178	0.781 (0.1793)	177	0.757 (0.1934)
	4th line	29	0.715 (0.2249)	33	0.679 (0.2231)
Week 8	3rd line	158	0.756 (0.2096)	163	0.762 (0.1850)
	4th line	19	0.765 (0.2009)	30	0.687 (0.2948)
Week 12	3rd line	114	0.778 (0.1918)	114	0.767 (0.1885)
	4th line	13	0.775 (0.2472)	23	0.716 (0.2328)
Week 16	3rd line	116	0.769 (0.1715)	127	0.774 (0.1790)
	4th line	18	0.808 (0.1350)	22	0.742 (0.1828)
Week 20	3rd line	3	0.818 (0.2385)	1	0.767 (NA)
	4th line	0	NA	0	NA
Week 24	3rd line	68	0.776 (0.1590)	87	0.767 (0.2049)
	4th line	11	0.750 (0.2264)	17	0.660 (0.3341)
Week 28	3rd line	1	0.645 (NA)	1	1.00 (NA)
	4th line	0	NA	0	NA
Week 32	3rd line	38	0.743 (0.2425)	51	0.827 (0.1516)
	4th line	8	0.699 (0.1565)	13	0.751 (0.1078)

		Avapritinib (60)		Regorafenib (60)	
		N	Mean (SD)	N	Mean (SD)
Week 36	3rd line	2	0.760 (0.1089)	1	0.449 (NA)
	4th line	0	NA	1	0.750 (NA)
Week 40	3rd line	20	0.810 (0.1455)	38	0.790 (0.1470)
	4th line	7	0.794 (0.1350)	8	0.728 (0.1985)
Week 44	3rd line	1	0.735 (NA)	1	1.00 (NA)
	4th line	0	NA	0	NA
Week 48	3rd line	14	0.798 (0.1279)	29	0.811 (0.1679)
	4th line	7	0.799 (0.1305)	7	0.744 (0.1478)
Week 52	3rd line	1	0.821 (NA)	1	0.795 (NA)
	4th line	0	NA	0	NA
Week 56	3rd line	5	0.792 (0.1518)	11	0.847 (0.1330)
	4th line	1	0.679 (NA)	2	0.701 (0.0311)
Week 60	3rd line	1	0.654 (NA)	0	NA
	4th line	0	NA	0	NA
Week 64	3rd line	3	0.807 (0.1770)	8	0.840 (0.1440)
	4th line	0	NA	1	0.654 (NA)
Week 72	3rd line	0	NA	2	1.00 (NA)
	4th line	0	NA	1	1.00 (NA)
Week 80	3rd line	0	NA	0	NA
	4th line	0	NA	1	0.879 (NA)

Abbreviations: SD: standard deviation, NA: not applicable

10.3.4 HSUV and disutility results

HSUVs for the overall ITT population from the VOYAGER study at baseline for patients treated at third and fourth line are presented in Table 43.

Table 43 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
SoC2	0.782 (NA)	EQ-5D-5L	UK	Estimate is based on mean of both trial arms of 3rd line (81).
PD	0.727 (NA)	EQ-5D-5L	UK	Estimate is based on mean of both trial arms of 4th line (81).

Abbreviations: HSUV: health state utility value, SoC: standard of care, PD: progressed disease, EQ-5D-5L: EuroQol 5-Dimension, NA: not applicable.

Table 44 Overview of literature-based health state utility values

	Results [SD]	Instrument	Tariff (value set) used	Comments
Avapritinib, first line				
TA86/209	0.935 (0.094)	ECOG	UK	Utility values for patients in the imatinib arm in the CST1571-B2222 trial was estimated by a mapping of ECOG performance status to EQ5D scores by 3 clinicians (56, 72).
SoC1				
TA179	0.781 (0.780)	EQ-5D	UK	EQ-5D data was collected in the A618100447 trial (64).
Disutilities (only applied in scenario analysis)				
See Table 37				

Abbreviations: SD: standard deviation, TA: technology appraisal, SoC: standard of care, ECOG: Eastern Cooperative Oncology Group, EQ-5D: EuroQol-5 dimension.

11. Resource use and associated costs

Costs and resource use vary dependent on the administered treatment and health states. The model includes direct medical costs, as well as transport costs and time spent on treatment by patients, consistent with the restricted societal perspective as described in the DMC guidelines (3). All costs were valued in 2023 Danish Krone (DKK).

The following section regarding cost and resource use is presented per health state, containing information regarding drug acquisition costs, disease management costs and AE costs. Drug costs are sourced from Medicinpriser.dk (46) and applied as pharmacy purchasing prices (AIP). Disease management and AE costs are based on Danish diagnosis related groups (DRG) tariffs from 2023 (82) and DMC catalogue for unit costs (83). Patient and transportation costs are based on the DMC catalogue for unit costs and are presented in a separate section covering all patient- and transportation costs for all health states (83).

11.1 Pharmaceutical costs (intervention and comparator)

As all the pharmaceuticals included in the model are oral therapies, no wastage of pharmaceuticals was accounted for in the calculations. The pharmaceutical costs are assumed to be incurred according to the time on treatment curve (for the avapritinib arm) and progression-free survival curves (for the ECM arm). Additional details are presented in Appendix D. Table 45 shows the pharmaceutical costs used in the model for avapritinib and ECM. The costs are pharmacy purchase price, Apotekernes indkøbspris (AIP), derived from Medicinpriser.dk (46).

Avapritinib

Avapritinib is an oral therapy available as tablets containing 100, 200, or 300 mg, all with the same list price of 136,662.16 DKK per pack of 30 tablets, informed by Blueprint Medicines (7). The dosing regimen of avapritinib is 300 mg once daily and is aligned with the recommended starting dose of avapritinib and the NAVIGATOR trial (8). For the purposes of modelling, the 300mg tablets are used, to align with the recommended starting dose.

ECM

ECM consists of TKIs (imatinib, sunitinib, and regorafenib). The proportion of patients receiving each therapy is based on clinical expert statements suggesting a split of 20% on imatinib, 0% on sunitinib, and 0% on regorafenib (45). This is used for the base case (52). The dosing regimen of ECM is based on previous TAs (56-58, 84).

Table 45 Pharmaceutical costs used in the model

Pharmaceutical		Strength	Package size	Pharmacy purchase price [DKK]
Avapritinib		100mg	30 tablets	XXXXXXXX (46)
		200mg	30 tablets	XXXXXXXX (46)
		300mg	30 tablets	XXXXXXXX (46)
TKIs	Imatinib	400mg	30 tablets	12,870.00
	Sunitinib	50mg	28 tablets	1674.01
	Regorafenib	40mg	84 tablets	19,650.36

Abbreviations: TKI: tyrosine kinase inhibitor, mg: milligrams, DKK: Danish Krone,

11.2 Pharmaceutical costs – co-administration

Not applicable.

11.3 Administration costs

No administration costs are used as the treatments considered in both the intervention and comparator arms are all oral therapies.

Table 46 Administration costs used in the model – not applicable

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

Abbreviations: NA = not applicable; DRG = diagnosis-related group, DKK: Danish Krone.

11.4 Disease management costs

Unresectable or metastatic PDGFRA D842V-mutated GIST is unlikely to significantly differ from general unresectable or metastatic GIST in terms of disease management HCRU costs outside of treatment cost. Little information on this is available in the literature. Based on

HCRU cost values from the most recent NICE GIST technology appraisal, TA488 (committee papers, section 2.4), obtained by a panel of UK clinical experts, resource use frequencies are considered as a starting point for this analysis (59). These estimates then underwent validation by a clinical expert and, when advised, were adjusted to align with Danish clinical practice (38, 52). In the economic model, the resource use is split into PF health states and PD and applied as a one-off and a per cycle cost. Disease management unit costs are presented in Table 47 and Table 48 for PF and PD.

Table 47 Disease management costs used in the model.

Activity		Frequency	% of patients receiving	Unit cost [DKK]	DRG code/ element	Reference
CT-scan	PF	Every 3rd week	80%	2,400	30PR06, <12 hours	DRG 2023 (82)
	PD	Every 2.5th week				
MRI scan	PF	Every 5th week	20%	2,447	30PR02, <12 hours	DRG 2023 (82)
	PD	Every 2.5th week				
Full blood count	PF	Every 4th week	100%	21.63	Lab test	Takstkort, Laeger.dk (85)
	PD	Every 2.5th week				
Liver function test	PF	Every 4th week	100%	67.00	P-ASAT, P-ALAT, P-ALP, P-Bilirubin, P-GT	Labportal.rh.dk (86)
	PD	Every 2.5th week				
Outpatient visit	PF	Every 4th week	25%	147.85	Consultation	Medicinraadet, unit cost catalogue (83)
	PD	Every 2.5th week	100%			
Palliative resection	PF	a	10%	118,343	06MP10	DRG 2023 (82)
	PD	a	15%			
Palliative radiotherapy	PF	a	5%	2,600	27MP04	DRG 2023 (82)
	PD	a				

Abbreviations: DRG = diagnosis-related group; PF = progression free; PD = progressed disease; CT = computed tomography; MRI = magnetic resonance imaging.

Notes: a = palliative resection and palliative radiotherapy is applied as one-off cost

Table 48 Disease management costs used in the model (pain management).

Intervention		Frequency	% of patients receiving	Per cycle cost [DKK]	Reference (87)
Co-comadol	PF	8 per day	5%	58.34	Medicinpriser.dk
	PD		10%		
Tramadol	PF	8 per day	NA	7.90	

Intervention		Frequency	% of patients receiving	Per cycle cost [DKK]	Reference (87)
	PD		NA		Medicinpriser.dk(87)
Paracetamol	PF	8 per day	30%	16.71	Medicinpriser.dk
	PD				
Morphine	PF	2 per day	NA	9.64	Medicinpriser.dk
	PD		NA		
Dexamethasone	PF	Every 3rd week	NA	175.85	Medicinpriser.dk
	PD	Every 2.5th week	NA		
Betamethasone	PF	Every 3rd week	NA	88.00	Medicinpriser.dk
	PD	Every 2.5th week	10%		
Oxicodon	PF	2 per day	10%	29.15	Medicinpriser.dk
	PD		25%		

Abbreviations: PF = progression-free; PD = progressed disease, DKK: Danish Krone,

11.5 Costs associated with management of adverse events

Unit costs of adverse events associated with both treatment arms are presented in Table 49. The model captures the costs associated with the management of treatment-related grade 3+ AEs. Frequencies of grade 3+ AEs incurred in both arms are presented in section 9.2. Assumption on duration of AEs is above 12 hours, meaning that all costs are assumed to be carried out in inpatient settings and are costed from the Danish DRG tariffs platform (82).

The model assumes that patients receiving avapritinib incur these costs only in the first line, i.e., when they receive avapritinib. Upon discontinuation, patients in the avapritinib arm do not incur any costs associated with AE management.

Any AEs reported in NAVIGATOR that were used in the model but were not reported for the comparator were assumed to have 0% incidence for the comparator; these were therefore not costed. This is conservative, meaning that more AEs are costed within the avapritinib arm.

Table 49 Cost associated with management of adverse events

	DRG code (82)	Unit cost/DRG tariff (82)
Abdominal pain	06MA11	7,530.00
Abnormal liver function results	23MA03	4,278.00
Anaemia	16MA05	40,106.00

	DRG code (82)	Unit cost/DRG tariff (82)
Ascites	07MA03	27,085.00
Asthenia	23MA03	4,728.00
Blood bilirubin increased	Set to 0, Overlapping with ”Abnormal liver function results”	
Confusional state	01MA17	26,400.00
Decreased appetite	10MA04	20,850.00
Diarrhoea	06MA11	7,530.00
Dermatitis / rash	09MA03	19,941.00
Dyspnoea	04MA23	21,632.00
Fatigue	23MA03	4,728.00
Oedema	23MA03	4,728.00
Haemorrhage	05MA08	2,089.00
Hypertension	05MA11	17,304.00
Hypokalaemia	10MA06	26,368.00
Hyponatremia	10MA06	26,368.00
Hypophosphatemia	10MA02	39,158.00
Leukopenia	16MA10	26,179.00
Lymphopenia	16MA10	26,179.00
Nausea	06MA11	7,530.00
Neutropenia	16MA03	38,209.00
Neutrophil count decreased	Set to 0, Overlapping with ”Neutropenia”	
Pleural effusion	04MA09	36,350.00
Hypocalcaemia	10MA02	39,158.00
Clostridium difficile infection	16MA11	7,530.00
Disease progression	06MA02	37,945.00

Abbreviations: DRG = diagnosis-related group

11.6 Subsequent treatment costs

Not applicable.

11.7 Patient costs

Patient costs for transportation and time have been included based on the requirements from the DMC (53). Frequency of healthcare visits were based on the most recent NICE GIST technology appraisal, TA488 (committee papers, section 2.4) and clinical expert statements (59) (52). It was assumed that each visit would take an average of 2 hours patient time

including transportation time. The value of patients' time was DKK 203 per hour, and travel expenses were assumed to be DKK 140 per roundtrip, as per DMC's unit cost catalogue (83). To estimate patient costs for both the PF and PD state, the time usage presented in Table 50 was assumed.

Table 50 Patient costs used in the model

Activity	Time spent [minutes]
Patient time associated with outpatient consultation including blood test and liver function test	60 minutes per visit.
Patient time associated with CT scan	60 minutes per visit.
Patient time associated with MRI scan	60 minutes per visit.

Abbreviations: CT = computed tomography, MRI = magnetic resonance imaging

It has been assumed that certain tests and visits can be combined during a single outpatient appointment, therefore the outpatient visit will include a full blood count as well as a liver function test. This grouping assumes that these elements can be conducted within a combined timeframe of 60 minutes. Furthermore, it is assumed that CT scan and MRI scan are considered individually due to their distinct imaging techniques and purposes. Since it is assumed that patients spend 1 hour per visit, this is corresponding to a cost of 501 DKK per health care visit. Based on the weighted frequency of resource use reported in Table 47, the total costs per month for PF and PD is 277.78 DKK and 401.12 DKK, respectively.

11.8 Other costs (palliative care cost)

Not applicable.

12. Results

12.1 Base case overview

The key aspects of the base case cost-effectiveness model are presented in Table 51.

Table 51 Base case overview

Feature	Description
Comparator	ECM (TKIs consisting of imatinib, sunitinib and regorafenib) and best supportive care.
Type of model	State transition model
Time horizon	Lifetime
Treatment line	1st line. Subsequent treatment lines not included.
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in the VOYAGER trial (6). Utility values for first line and SoC1 were sourced from previous NICE TAs (56-58).
Costs included	Pharmaceutical costs

Feature	Description
	Disease management costs Costs of adverse events Patient costs
Dosage of pharmaceutical	Fixed dosage of avapritinib
Average time on treatment	**Avapritinib:** XXXXXXXX, **ECM:** XXXXXXXX
Parametric function for PFS	Avapritinib: Weibull, ECM: Weibull
Parametric function for OS	Avapritinib: Lognormal, ECM: Weibull
Inclusion of waste	No
Average time in model health state **Ava / 1L** **SoC1** **SoC2** **PD**	Avapritinib: XXXXXXXX / ECM: XXXXXXXX Avapritinib: XXXXXXXX / ECM: XXXXXXXX Avapritinib: XXXXXXXX / ECM: XXXXXXXX Avapritinib: XXXXXXXX / ECM: XXXXXXXX

12.1.1 Base case results

In the model base case where avapritinib is compared against ECM (consisting of TKIs: imatinib, sunitinib, and regorafenib), discounted results are presented in Table 52. Using a lifetime horizon (40 years), the incremental expected total life-year gain amounts to XXXXXXXX years (discounted). The discounted incremental costs of XXXXXXXX DKK and incremental QALYs of XXXXXXXX resulted in an incremental cost-effectiveness ratio (ICER) of XXXXXXXX DKK / QALY versus ECM.

Table 52 Base case results, discounted estimates

	Avapritinib	ECM	Difference
Pharmaceutical costs	XXXXXXXX	XXXXXXXX	XXXXXXXX
Pharmaceutical costs – co-administration	NA	NA	NA
Administration	NA	NA	NA
Disease management costs	XXXXXXXX	XXXXXXXX	XXXXXXXX
Costs associated with management of adverse events	XXXXXXXX	XXXXXXXX	XXXXXXXX
Subsequent treatment costs	NA	NA	NA
Patient costs	XXXXXXXX	XXXXXXXX	XXXXXXXX
Palliative care costs	NA	NA	NA
Total costs	XXXXXXXX	XXXXXXXX	XXXXXXXX
Life years gained, Ava / first line	XXXXXXXX	XXXXXXXX	XXXXXXXX
Life years gained, SoC1	XXXXXXXX	XXXXXXXX	XXXXXXXX
Life years gained, SoC2	XXXXXXXX	XXXXXXXX	XXXXXXXX

	Avapritinib	ECM	Difference
Life years gained, PD	XXXXXXXX	XXXXXXXX	XXXXXXXX
Total life years	XXXXXXXX	XXXXXXXX	XXXXXXXX
QALYs, Ava / first line	XXXXXXXX	XXXXXXXX	XXXXXXXX
QALYs, SoC1	XXXXXXXX	XXXXXXXX	XXXXXXXX
QALYs, SoC2	XXXXXXXX	XXXXXXXX	XXXXXXXX
QALYs, PD	XXXXXXXX	XXXXXXXX	XXXXXXXX
QALYs (adverse reactions)	XXXXXXXX	XXXXXXXX	XXXXXXXX
Total QALYs	XXXXXXXX	XXXXXXXX	XXXXXXXX

Incremental costs per life year gained:

XXXXXXXX **DKK/ LY**

Incremental cost per QALY gained (ICER):

XXXXXXXX **DKK/QALY**

12.2 Sensitivity analyses

Parameter uncertainty was investigated both deterministically and probabilistically. Full details of parameter specifications, including details of how they varied in the model can be found in Appendix G.

12.2.1 Deterministic sensitivity analyses

Univariate parameter uncertainty was tested using univariate sensitivity analysis, in which all model parameters were systematically and independently varied over a plausible range determined by ±10%. The 10 most influential model parameters with regards to impact on range of impact on the base case ICER are presented in Table 53, and as a tornado diagram in Figure 21.

Table 53 One-way sensitivity analyses results

	Change	Reason/Rational/ Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	0%	NA	XXXXXXXX	XXXXXXXX	XXXXXXXX
Discount rate outcomes 3.5% - lower value	XXXXXXXX	Range of impact on the base case ICER	XXXXXXXX	XXXXXXXX	XXXXXXXX
Discount rate outcomes 3.5% - upper value	XXXXXXXX	Same as above	XXXXXXXX	XXXXXXXX	XXXXXXXX
Utility PF 1L – lower value	XXXXXXXX	Same as above	XXXXXXXX	XXXXXXXX	XXXXXXXX

	Change	Reason/Rational/ Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Utility PF 1L – upper value	XXXXXXXX	Same as above	XXXXXXXX	XXXXXXXX	XXXXXXXX
Discount rate costs 3.5% - lower value	XXXXXXXX	Same as above	XXXXXXXX	XXXXXXXX	XXXXXXXX
Discount rate costs 3.5% - upper value	XXXXXXXX	Same as above	XXXXXXXX	XXXXXXXX	XXXXXXXX
Initial age (years) - lower value	XXXXXXXX	Same as above	XXXXXXXX	XXXXXXXX	XXXXXXXX
Initial age (years) - upper value	XXXXXXXX	Same as above	XXXXXXXX	XXXXXXXX	XXXXXXXX
Utility PF 3L – lower value	XXXXXXXX	Same as above	XXXXXXXX	XXXXXXXX	XXXXXXXX
Utility PF 3L – upper value	XXXXXXXX	Same as above	XXXXXXXX	XXXXXXXX	XXXXXXXX
Utility PF 2L – lower value	XXXXXXXX	Same as above	XXXXXXXX	XXXXXXXX	XXXXXXXX
Utility PF 2L – upper value	XXXXXXXX	Same as above	XXXXXXXX	XXXXXXXX	XXXXXXXX
Utility PD – lower value	XXXXXXXX	Same as above	XXXXXXXX	XXXXXXXX	XXXXXXXX
Utility PD - upper value	XXXXXXXX	Same as above	XXXXXXXX	XXXXXXXX	XXXXXXXX
Management cost, PF w/ 1st, 2nd, and 3rd line (per cycle) – lower value	XXXXXXXX	Same as above	XXXXXXXX	XXXXXXXX	XXXXXXXX
Management cost, PF w/ 1st, 2nd, and 3rd line (per cycle) – upper value	XXXXXXXX	Same as above	XXXXXXXX	XXXXXXXX	XXXXXXXX
Management cost, PD (per cycle) – lower value	XXXXXXXX	Same as above	XXXXXXXX	XXXXXXXX	XXXXXXXX
Management cost, PD (per	XXXXXXXX	Same as above	XXXXXXXX	XXXXXXXX	XXXXXXXX

	Change	Reason/Rational/ Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
cycle) – upper value					
Incidence, Anaemia, avapritinib – lower value	XXXXXXXX	Same as above	XXXXXXXX	XXXXXXXX	XXXXXXXX
Incidence, Anaemia, avapritinib – upper value	XXXXXXXX	Same as above	XXXXXXXX	XXXXXXXX	XXXXXXXX

Figure 21 Tornado diagram

A number of scenarios were considered in the deterministic sensitivity analyses exploring variations from the base model settings (Table 51). Important factors for estimating the ICER of treatment of GIST patients harbouring the PGDFRA D842V mutation with avapritinib include the proportion of patients receiving TKIs in the ECM arm and choice of utility value source. If patients are not prescribed any TKIs (0%), this will have a minor impact on the ICER. Danish-mapped EQ-5D-5L tariffs were applied to SoC2 and PD health states, despite potential inconsistency with the remaining HSUV due to infeasibility of applying Danish weights. Furthermore, to match AVA/1L HSUV with a Danish general population utility this was explored in scenario analyses. Table 54 presents the scenario analyses.

Table 54 Scenario analyses

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	0%	NA	XXXXXXXX	XXXXXXXX	XXXXXXXX

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
ECM: 0% IMA, SUN, REG	XXXX XXXX	Due to lack of recommendations on clinical treatment guideline	XXXXXXX X	XXXXXXXX	XXXXXXXX
ECM: 100% IMA, SUN, REG	XXXX XXXX	BLU-285-1002 mix	XXXXXXX X	XXXXXXXX	XXXXXXXX
Utilities in SoC2 and PD with EQ-5D-5L DK tariffs	XXXX XXXX	DMC method guide, DK tariffs	XXXXXXX X	XXXXXXXX	XXXXXXXX
Utility in Ava/1L with 0.832	XXXX XXXX	Danish age matched population & ERG comment from NICE TA730 (committee papers, section 4.2.7.2)	XXXXXXX X	XXXXXXXX	XXXXXXXX
Utility decrements applied	XXXX XXXX	DMC preference	XXXXXXX X	XXXXXXXX	XXXXXXXX
Survival for ECM arm: Cassier et al.	XXXX XXXX	Alternative comparator arm	XXXXXXX X	XXXXXXXX	XXXXXXXX
AE incidence data based on full population	XXXX XXXX	To align with modelled population (safety population).	XXXXXXX X	XXXXXXXX	XXXXXXXX
Avapritinib OS extrapolation: Weibull	XXXX XXXX	Alternative curve fitting and NICE TSD 14	XXXXXXX X	XXXXXXXX	XXXXXXXX
ECM OS extrapolation: Exponential	XXXX XXXX	Alternative curve fitting and NICE TSD 14	XXXXXXX X	XXXXXXXX	XXXXXXXX
Avapritinib PFS extrapolation: Exponential	XXXX XXXX	Alternative curve fitting and NICE TSD 14	XXXXXXX X	XXXXXXXX	XXXXXXXX
ECM PFS extrapolation: Exponential	XXXX XXXX	Alternative curve fitting and NICE TSD 14	XXXXXXX X	XXXXXXXX	XXXXXXXX

12.2.2 Probabilistic sensitivity analyses

A scatter plot of 1,000 simulations, including a 95% confidence cloud, is presented in Figure 22, with a cost-effectiveness acceptability curve presented in Figure 23. The full set of parameters included in the model, including details of distributional forms, are presented in Appendix G.

Figure 22 Scatter plot of 1,000 simulations

Figure 23 Cost-effectiveness acceptability curve

13. Budget impact analysis

The budget impact model is developed to estimate the expected budget impact of recommending avapritinib for treatment of PGDFRA D842V mutated GIST in Denmark. The budget impact analysis has been embedded within the cost-effectiveness model and therefore any changes in the settings of the cost per patient model would affect the results of the budget impact model. The budget impact result is representative of the populations in the cost per patient model. The costs included in the budget impact model are undiscounted, and patient cost and transportation cost have not been included as per the guidelines by the DMC (53).

The analysis is developed by comparing the costs for the Danish regions per year over five years in the scenario where avapritinib is recommended as a standard treatment and the scenario where avapritinib is not recommended as a standard treatment. The total budget impact per year is the difference between the two scenarios.

13.1 Number of patients (including assumptions of market share)

As discussed in 3.2, only one case of PDGFRA D842V mutated GIST (treated with avapritinib) is known in Denmark with an estimated incidence of 1 eligible patients every second year, see Table 55 (38). The budget impact analysis assumes that only incident patients, i.e., newly diagnosed patients will be treated with avapritinib if it is recommended (as reported in Table 1). Based on Dutch registry study (Steeghs et al 2021), it is expected that 80% of eligible patients receive targeted treatment. Therefore, the budget impact analysis assumes that if recommended, 80% of new eligible patients will receive avapritinib if avapritinib is recommended (80% market share of newly eligible patients) (88).

Table 55 Number of new patients expected to be treated over the next five-year period avapritinib is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
Recommendation					
Avapritinib	1	1	2	2	2
ECM	0	0	0	0	0
Non-recommendation					
Avapritinib	0	0	0	0	0
ECM	1	1	2	2	2

13.2 Budget impact

By comparing the costs for the Danish healthcare system per year over five years in the scenario where avapritinib is recommended as standard treatment and the scenario where avapritinib is not recommended as standard treatment. The total budget impact per year is the difference between the two scenarios.

The budget impact estimated in Table 56 is based on non-discounted cost outputs (2023 DKK) from the cost-effectiveness model for five years, and the assumed eligible patients described above, as well as the assumed uptake of avapritinib for the treatment of eligible PDGFRA D842V mutant GIST patients described above.

Table 56 Expected budget impact of recommending avapritinib in PDGFRA D842V mutant GIST

	Year 1	Year 2	Year 3	Year 4	Year 5
Avapritinib is recommended	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX
Avapritinib is NOT recommended	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX
Budget impact of the recommendation	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX

14. List of experts

Doctor Mikael Eriksson, Principal investigator at Lund University Cancer Centre and associate professor at medical oncology was consulted during the development of this application.

Doctor Sebastian Bauer, Professorship for personalized tumour therapy and specialist in internal medicine, haematology, and oncology. Internal clinic (tumour research) Essen University Hospital was consulted during the development of this application.

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Appendix A. Main characteristics of studies included

Table 57 Main characteristic of studies included

Trial name: NAVIGATOR (BLU-285-1101)	NCT number: NCT02508532
Objective	This is a Phase 1, open-label, first-in-human (FIH) study designed to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and antineoplastic activity of avapritinib (formerly BLU-285), administered orally, in adult patients with unresectable GIST or other relapsed or refractory solid tumours. The study consists of 2 parts, a dose-escalation part (Part 1) and an expansion part (Part 2) (54).
Publications – title, author, journal, year	• Jones RL, Serrano C, von Mehren M, George S, Heinrich MC, Kang YK, Schoffski P, Cassier PA, Mir O, Chawla SP, Eskens FALM, Rutkowski P, Tap WD, Zhou T, Roche M, Bauer S. Avapritinib in unresectable or metastatic PDGFRA D842V-mutant gastrointestinal stromal tumours: Long-term efficacy and safety data from the NAVIGATOR phase I trial. Eur J Cancer. 2021 Mar;145:132-142. doi: 10.1016/j.ejca.2020.12.008. Epub 2021 Jan 16. • Heinrich MC, Jones RL, von Mehren M, Schoffski P, Serrano C, Kang YK, Cassier PA, Mir O, Eskens F, Tap WD, Rutkowski P, Chawla SP, Trent J, Tugnait M, Evans EK, Lauz T, Zhou T, Roche M, Wolf BB, Bauer S, George S. Avapritinib in advanced PDGFRA D842V-mutant gastrointestinal stromal tumour (NAVIGATOR): a multicentre, open-label, phase 1 trial. Lancet Oncol. 2020 Jul;21(7):935-946. doi: 10.1016/S1470-2045(20)30269-2. Erratum In: Lancet Oncol. 2020 Sep;21(9):e418.
Study type and design	NAVIGATOR is a Phase 1, open-label, single-arm, multicentre, dose escalation and dose expansion clinical study evaluating the safety and efficacy of avapritinib in adult patients with unresectable or metastatic GIST, including a cohort of patients with the PDGFRA D842V mutation (Group 2), which is the focus of this submission. The study was completed on the 3rd of June 2021 (54). The study was divided into two parts. Part 1 was a dose-escalation study to determine the maximum tolerated dose or the recommended dose of avapritinib, and Part 2 was an expansion study to determine the safety and efficacy of avapritinib at the selected dose in adult patients with unresectable or metastatic GIST. The study was divided into three groups: • Patients with unresectable GIST that had progressed following treatment with imatinib and at least one of the following: sunitinib, regorafenib, sorafenib, dasatinib, pazopanib, or an experimental tyrosine kinase inhibitor therapy, and who did not have a D842V mutation in PDGFRA (Group 1)

Trial name: NAVIGATOR (BLU-285-1101)	NCT number: NCT02508532
	• Patients with unresectable GIST harbouring a D842V mutation in the PDGFRA gene, identified by local and central assessment, either in archival tissue or a new tumour biopsy obtained, prior to treatment with avapritinib (Group 2) • Patients with unresectable GIST that had progressed or those who had experienced intolerance following treatment with imatinib (including in the adjuvant setting) and who had not received additional kinase inhibitor therapy and did not have a known D842V mutation in PDGFRA (Group 3)
Sample size (n)	n = 250 (safety population) n = 56 (all doses of avapritinib for subgroup of GIST patients harbouring the PDGFRA D842V mutation) n = 38 (300 mg/400 mg dose of avapritinib for subgroup of GIST patients harbouring the PDGFRA D842V mutation)
Main inclusion criteria	For Part 1: • Histologically- or cytologically confirmed diagnosis of unresectable GIST or another advanced solid tumour. Patients with unresectable GIST must have disease that has progressed following imatinib and at least 1 of the following: sunitinib, regorafenib, sorafenib, dasatinib, pazopanib or an experimental kinase-inhibitor agent, or disease with a D842V mutation in the PDGFRα gene. Patients with an advanced solid tumour other than GIST must have relapsed or refractory disease without an available effective therapy. OR For Part 2: • Group 1: Patients must have a confirmed diagnosis of unresectable GIST that has progressed following imatinib and at least 1 of the following: sunitinib, regorafenib, sorafenib, dasatinib, pazopanib, or an experimental kinase-inhibitor agent, and the patient does not have a D842V mutation in PDGFRα. • Group 2: Patients must have a confirmed diagnosis of unresectable GIST with a D842V mutation in the PDGFRα gene. The PDGFRα mutation will be identified by local or central assessment, either in an archival tissue sample or a new tumour biopsy obtained prior to treatment with avapritinib. • Group 3: Patients must have a confirmed diagnosis of unresectable GIST that has progressed and/or patients must have experienced intolerance to imatinib and not received additional kinase-inhibitor therapy. Patients must not have a known D842V mutation in PDGFRα. • Groups 1, 2 and 3: At least 1 measurable lesion defined by mRECIST 1.1 for patients with GIST. • Groups 1 and 2: A tumour sample (archival tissue or a new tumour biopsy) has been submitted for mutational testing.

Trial name: NAVIGATOR (BLU-285-1101)		NCT number: NCT02508532
	• Eastern Cooperative Oncology Group (ECOG) performance status of 0-2	
Main exclusion criteria	• QT interval corrected using Fridericia's formula (QTcF) >450 milliseconds • Platelet count <90,000/mL • Absolute neutrophil count <1000/mL • Haemoglobin <9 g/dL • Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 x the upper limit of normal (ULN) if no hepatic metastases are present; >5 × ULN if hepatic metastases are present • Total bilirubin >1.5 × ULN; >3 × ULN with direct bilirubin, >1.5 × ULN in the presence of Gilbert's Disease • Estimated (Cockcroft-Gault formula) or measured creatinine clearance <40 mL/min Brain malignancy or metastases to the brain • History of a seizure disorder or requirement for anti-seizure medication • Group 3: Patients known to be KIT wild type	
Intervention	The dose escalation cohorts of the trial will not be included here as it did not inform on the safety and efficacy of avapritinib. Instead, only the cohort which assessed the safety and efficacy of avapritinib is presented below: Experimental: Part 1 and Part 2 avapritinib 300 mg or 400 mg QD Part 1 and Part 2: Patients enrolled in Part 1 and Part 2 at a starting dose of 300 or 400 mg QD were included in the Part1/Part 2 safety and efficacy analysis. Patients received avapritinib in continuous 28-day cycles until discontinuation.	
Comparator(s)	No comparator as NAVIGATOR is a single-arm trial.	
Follow-up time	Median follow-up of 25.5 months for the PDGFRA D842 subpopulation receiving avapritinib 300/400 mg. Median OS follow was 33.1 months for the PDGFRA D842 subpopulation receiving avapritinib 300/400 mg.	
Is the study used in the health economic model?	Yes.	
Primary, secondary and exploratory endpoints	**Primary outcomes measures:** 1. Part 1: Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose (RP2D) of Avapritinib	

Patients with event(s) of dose-limiting toxicity

2. Parts 1 and 2: Number of Patients With Adverse Events (AE) and Serious Adverse Events (SAE)

   The overall safety profile of the drug was assessed by reviewing the number of patients with AEs, SAEs and other events. There was no formal statistical analysis. Safety assessments continued for the duration of treatment.

3. Part 2: Objective Response Rate (ORR) Determined by Central Radiology Assessment Per mRECIST, Version 1.

   To evaluate objective response rate (ORR) determined by central radiology assessment per mRECIST, version 1.1 in patients with advanced GIST treated with avapritinib. A complete response per modified Response Evaluation Criteria In Solid Tumours Criteria (RECIST v1.1) is defined as complete disappearance of all target lesions. A partial response is defined as at least 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum of diameters. Overall Response (OR) = CR + PR

Secondary outcome measures:

1. Maximum Plasma Drug Concentration (Cmax)

   Maximum plasma drug concentration (Cmax) following a single dose of avapritinib

2. Time to Maximum Plasma Drug Concentration (Tmax)

   Cycle 1 Day 1 PK time to maximum plasma drug concentration (Tmax)

3. Plasma Drug Concentration at 24 Hours Postdose Prior to the Next Daily Dose (C24)

   Plasma drug concentration at 24 hours postdose prior to the next daily dose (C24) following a single dose of avapritinib

4. Area Under the Plasma Concentration-time Curve from time 0 to 24 Hours (AUC 0-24)

   Area under the plasma concentration-time curve from time 0 to 24 hours (AUC 0-24) following a single dose of avapritinib

5. Apparent Oral Clearance Unadjusted for Bioavailability (CL/F)

   Apparent oral clearance unadjusted for bioavailability (CL/F) following a single dose of avapritinib

6. Apparent Volume of Distribution, Unadjusted for Bioavailability (Vz/F)

   Apparent volume of distribution, unadjusted for bioavailability (Vz/F) following a single dose of avapritinib

7. Terminal Elimination Half-life (t1/2)

   Terminal elimination half-life (t1/2) following a single dose of avapritinib

8. Maximum Plasma Drug Concentration (Cmax) at Steady State

Maximum plasma drug concentration (Cmax) at steady state following 15 days of QD dosing

9. Time of Maximal Concentration (Tmax) at Steady State

   Time of maximal concentration (Tmax) at steady state following 15 days of QD dosing

10. Plasma Drug Concentration at 24 Hours Postdose Prior to the Next Daily Dose at Steady State (C24,ss)

    Plasma Drug Concentration at 24 Hours Postdose Prior to the Next Daily Dose at steady state (C24,ss) following 15 days of QD dosing

11. Area Under the Plasma Concentration-time Curve Over the Dosing Interval at Steady Sate (AUC0-τ,ss) (τ=24 h)

    Area under the plasma concentration-time curve over the dosing interval at steady sate (AUC0-τ,ss) (τ=24 h) following 15 days of QD dosing

12. Progression-free Survival Per mRECIST Version 1.1

    Progression-free survival is defined as the time in months from the start of treatment to the date of first documented progression or death due to any cause. Progression-free survival determined by central radiological assessment per modified Response Evaluation Criteria in Solid Tumours (mRECIST), version 1.1 in patients with advanced GIST. A progressively growing tumour must meet the following criteria: a) the target lesions must be greater or equal to 2cm in size and be a new GIST active lesion or b) the target lesions must be expanding on at least 2 sequential imaging studies.

13. Apparent Oral Clearance at Steady State, Unadjusted for Bioavailability (CLss/F)

    Apparent oral clearance at steady state, unadjusted for bioavailability (CLss/F) following 15 days of QD dosing

14. Clinical Benefit Rate Determined by Central Radiology Assessment Per mRECIST, Version 1.1

    Percent of patients with a complete response, partial response or stable disease lasting more than 16 weeks. A complete response per modified Response Evaluation Criteria In Solid Tumours Criteria (RECIST v1.1) is defined as complete disappearance of all target lesions. A partial response is defined as at least 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum of diameters. Stable disease is defined as a tumour that does not meet the criteria for progression or for response. A progressively growing tumour must meet the following criteria: a) the target lesions must be greater or equal to 2cm in size and be a new GIST active lesion or b) the target lesions must be expanding on at least 2 sequential imaging studies.

15. Response Rate Determined by Central Radiology Assessment Per Choi Criteria

A complete response is defined as complete disappearance of all target lesions. A partial response is ≥10% decrease tumour size at computed tomography (CT) or ≥15% decrease in tumour attenuation at computed tomography (CT) and no new lesions. The response rate is defined as complete response plus partial response.

16. Duration of Response Determined by Central Radiology Assessment Per mRECIST, Version 1.1

    Duration from time to first documented CR/PR to date of first documented disease progression or death. A complete response per modified Response Evaluation Criteria In Solid Tumours Criteria (RECIST v1.1) is defined as complete disappearance of all target lesions. A partial response is defined as at least 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum of diameters. Overall Response (OR) = CR + PR

17. Median PFS on Last Prior Anti-cancer Therapy

    Progression Free Survival (PFS) is defined as the time in months from the start of treatment to the date of first documented disease progression or death due to any cause, which ever occurs first. PFS on last prior anti-cancer therapy is defined as the time in months from the start of last prior anti-cancer therapy to progression on that therapy.

18. Change From Baseline in Levels of KIT and PDGFRα Mutant Allele Fractions in Peripheral Blood

    Change of mutant allele fraction (MAF) summarizes the largest fold change. Change from baseline only displayed for patients with pre and post treatment MAF measurements. A positive number represents an increase in MAF. Data is only provided for patients that had both a baseline measurement and an end of treatment measurement.

19. KIT, PDGFRA, and Other Cancer-relevant Mutations Present in Tumour Tissue at Baseline and EOT

    Change in mutations in tumour tissue at baseline and end of treatment (EOT). EOT tumour biopsies were optional and there were no EOT samples collected.

Method of analysis	All efficacy analyses were safety population analyses. **Analysis of primary efficacy outcome: ORR** The primary efficacy endpoint of ORR was defined as the proportion of patients with a confirmed best response of CR or PR, where CR or PR had to be confirmed at a subsequent assessment without intervening progression. The primary analysis of ORR was conducted by central radiology per mRECIST Version 1.1. ORR was estimated using frequency, percentage, and two-sided 95% CIs based on the exact binomial distribution (Clopper–Pearson) for the safety population.

Additionally, the best overall response following the hierarchical order of CR, PR, SD, PD and NE was tabulated for the prespecified subpopulations in the safety population.

Logistic regression was fitted to assess the effect of factors individually on the ORR, including starting dose, maximum daily dose level, dose intensity, age, ECOG status, size of largest tumour mass, etc., stratified by mutation type. Factors that were significant at the 0.2 level in univariable models were entered in the final multivariable model.

Analysis of secondary efficacy outcomes of interest

DoR: Defined as the time from first documented response (CR/PR) to the date of first documented disease progression or death due to any cause, whichever occurred first. The date of disease progression was based on central radiology assessment per mRECIST Version 1.1. Patients without confirmed CR or PR were excluded from this analysis. Patients who were still responding to treatment at the time of data cut-off were censored at their last valid assessment. The analysis was primarily based on the FDA Guidance for Cancer Trial Endpoints (89). The censoring rules based on the EMA guidelines were used as a sensitivity analysis (90).

DoR was analysed using KM methods and included the estimated median with two-sided 95% CI and 25th and 75th percentiles. DoR at specific timepoints (e.g. 3-, 6- and 12-month, etc.) was computed, along with the standard errors using Greenwood's formula.(91)

Sensitivity analysis was conducted for DoR based on investigator assessment per mRECIST Version 1.1, or central radiology assessment per Choi criteria for the safety population. Both FDA and EMA censoring rules were applied.

PFS: Defined as the time from the start of treatment to the date of first documented disease progression or death due to any cause, whichever occurred first. The date of disease progression was based on central radiology assessment per mRECIST Version 1.1. Specifically, if not all scans were done on the same date, the first scan date was used. If a patient had not had an event, PFS was censored at the date of last valid assessment that was stable or better.

The KM method was used to estimate the survival distribution function. The median PFS along with its two-sided 95% CI and 25th and 75th percentiles were estimated. In addition, the event rates (or event-free rates) at specific timepoints (e.g. 3-, 6- and 12-month, etc.) were computed, along with the standard errors using Greenwood's formula.(91) Survival curves using the KM method were presented.

A Cox proportional hazards model was used to estimate hazard ratios of factors such as starting daily dose, maximum daily dose level, dose intensity, age, ECOG status, size of largest tumour mass, etc., along with 95% CIs. The model was stratified by mutation type (exon 18 versus not). Factors that are significant at the 0.2 level in univariable models were entered into the final multivariable model. Unstratified analysis based on the safety population was conducted.

Trial name: NAVIGATOR (BLU-285-1101)	NCT number: NCT02508532

CBR: Defined as the proportion of patients with a confirmed CR/PR, or SD lasting for four cycles (16 weeks). The response was assessed per mRECIST Version 1.1 by central radiology and investigator. CBR was estimated using frequency, percentage, and two-sided 95% CIs based on the exact binomial distribution.

Analysis of exploratory efficacy outcomes of interest

OS: Defined as the time from the start of treatment to the date of death. Patients who died before or on the data cut-off date were considered to have had an OS event. Patients who did not have death recorded prior to or on the cut-off date were censored at the last date known alive. Last date known alive was defined as the last non-imputed date of any patient record prior to or on the data cut-off date in the clinical database. It could be the last visit date or last contact date that the patient was known to be alive.

The survival distribution of OS was estimated using the KM method. The median OS, along with its two-sided 95% CI and 25th and 75th percentiles, were estimated. In addition, the survival rate at specific timepoints (e.g., 3-, 6- and 12-month, etc.) were computed, along with the standard errors using Greenwood's formula.(91) The plots of survival curves using the KM method were presented. Unstratified Cox proportional hazards model of OS was fitted as a sensitivity analysis.

Time to response: Defined as the time from the start of treatment to the time the response criteria for CR or PR were first met per mRECIST Version 1.1. Patients without a confirmed CR or PR were excluded from this analysis. If all scans were not done on the same date, the response date was the date of the first assessment.

Summary statistics were presented by starting doses, and the time to response was compared between starting doses using the Wilcoxon rank sum test, with patients with the longest time to response having the highest rank.

Plot of cumulative probability of response was provided by starting dose.

Subgroup analyses

The patient population with the PDGFRA D842V mutation was a pre-specified subgroup of interest in the NAVIGATOR study. Additional subgroup analyses were not performed within this patient population.

The following subgroup analyses were conducted, using the March 2020 data cut, for ORR, DOR, PFS as assessed by central radiology, and OS, for safety subpopulations of PDGFRA exon 18 mutation, including D842V, and patients treated at fourth line and beyond; both limited to patients with starting dose of 300/400 mg:

- Age (< 65 years, ≥ 65 years)
- Gender (male, female)
- Region (US, Europe, Asian)
- Race (white, non-white)
- Largest target lesion (≤ 10 cm, > 10 cm)

Trial name: NAVIGATOR (BLU-285-1101)		NCT number: NCT02508532
	Corresponding forest plots were provided based on the odds ratio or hazard ratio for each subgroup.	
Other relevant information	None	

Appendix B. Efficacy results per study

Results per study

Results of the NAVIGATOR study are presented in the table below. All results for ORR, DOR, TTR, PFS and radiographic tumour reductions are based on the data cut from March 2020. Results for OS are based on the data cut from January 2021.

Table 58 presents the NAVIGATOR results for the PDGFRA D842V population who received 300 mg/400 mg dose of avapritinib (N=38). Table 59 presents the NAVIGATOR results for the PDGFRA D842V population who received all doses of avapritinib (N=56).

Table 58 Results per study for unresectable or metastatic GIST patients with PDGFRA D842V mutation; NAVIGATOR; avapritinib 300 mg/400 mg

Results of NAVIGATOR (BLU-285-1101, NCT02508532)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
ORR	Avapritinib	38	94.7% (82.3–99.4)	N/A	N/A	N/A	N/A	N/A	N/A	Best response assessed by central radiology using mRECIST Version 1.1. The proportion of patients with a confirmed best response of CR or PR.	
	N/A	N/A	N/A								
CR	Avapritinib	38	13.2% (4.4–28.1)	N/A	N/A	N/A	N/A	N/A	N/A	Best response assessed by central radiology using mRECIST Version 1.1.	
	N/A	N/A	N/A								

Results of NAVIGATOR (BLU-285-1101, NCT02508532)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
PR	Avapritinib	38	81.6% (65.7–92.3)	N/A	N/A	N/A	N/A	N/A	N/A	Best response assessed by central radiology using mRECIST Version 1.1.	
	N/A	N/A	N/A								
SD	Avapritinib	38	5.3% (0.6–17.7)	N/A	N/A	N/A	N/A	N/A	N/A	Best response assessed by central radiology using mRECIST Version 1.1.	
	N/A	N/A	N/A								
PD	Avapritinib	38	0% (0.0)	N/A	N/A	N/A	N/A	N/A	N/A	Best response assessed by central radiology using mRECIST Version 1.1.	
	N/A	N/A	N/A								
CBR	Avapritinib	38	97.4% (86.2–99.9)	N/A	N/A	N/A	N/A	N/A	N/A	Best response assessed by central radiology using mRECIST Version 1.1. Two-sided 95% CI based on exact binomial distribution using the Clopper–Pearson method. The proportion of patients with confirmed CR/PR or SD lasting ≥4 cycles from first dose date.	
	N/A	N/A	N/A								

Results of NAVIGATOR (BLU-285-1101, NCT02508532)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
DCR	Avapritinib	38	100.0% (90.7–100.0)	N/A	N/A	N/A	N/A	N/A	N/A	Best response assessed by central radiology using mRECIST Version 1.1. The proportion of patients with a confirmed best response of CR, PR, or SD.	
	N/A	N/A	N/A								
Median DOR	Avapritinib	36	22.1 (14.1– -) months	N/A	N/A	N/A	N/A	N/A	N/A	Duration of response by central radiology per mRECIST 1.1 and EMA Censoring Rule. Duration of Response is defined as the time in months from first documented response (CR/PR) to the date of first documented disease progression or death due to any cause, whichever comes first. Patients without confirmed CR or PR will be excluded from this analysis. Patients who are still in response at time of data cutoff will be censored at their last valid assessment. Confidence	
	N/A	N/A	N/A								
3-month DOR	Avapritinib	36	100 (100.0, 100.0)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
6-month DOR	Avapritinib	36	88.6 (78.0, 99.1)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
9-month DOR	Avapritinib	36	82.9 (70.4, 95.3)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								

Results of NAVIGATOR (BLU-285-1101, NCT02508532)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
12-month DOR	Avapritinib	36	74.2 (59.6, 88.7)	N/A	N/A	N/A	N/A	N/A	N/A	intervals are calculated using the linear transformation.	
	N/A	N/A	N/A								
18-month DOR	Avapritinib	36	58.8 (42.2, 75.5)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
24-month DOR	Avapritinib	36	43.3 (25.2, 61.3)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
30-month DOR	Avapritinib	36	32.5 (9.6, 55.3)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
36-month DOR	Avapritinib	36	32.5 (9.6, 55.3)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
Median Time to first response (Range)	Avapritinib	36	59.5 (52-757) days	N/A	N/A	N/A	N/A	N/A	N/A	Time to response is defined as the time in days from the start of treatment to the time the response criteria for CR or PR are first met per mRECIST Version 1.1. Patients without	
	N/A	N/A	N/A								

Results of NAVIGATOR (BLU-285-1101, NCT02508532)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										confirmed CR or PR will be excluded from this analysis.	
Median OS	Avapritinib	38	Not reached	N/A	N/A	N/A	N/A	N/A	N/A	OS was defined as the time from the start of treatment to the date of death. All patients who did not have a death record prior to or on the cut-off date were censored at either the data cut-off date or the last date known alive + 1, whichever occurred earlier.	
	N/A	N/A	N/A								
6-month OS KM estimate	Avapritinib	38	100.0 (100.0, 100.0)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
12-month OS KM estimate	Avapritinib	38	91.4 (82.2, 100.0)	N/A	N/A	N/A	N/A	N/A	N/A	Kaplan–Meier estimates with censoring at the earlier of the data cut-off date and the last date known alive + 1.	
	N/A	N/A	N/A								
18-month OS KM estimate	Avapritinib	38	88.6 (78.0, 99.1)	N/A	N/A	N/A	N/A	N/A	N/A	Progression-free survival per EMA censoring rule	
	N/A	N/A	N/A								
24-month OS KM estimate	Avapritinib	38	71.0 (55.9, 86.2)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
	Avapritinib	38	71.0 (55.9, 86.2)	N/A	N/A	N/A	N/A	N/A	N/A		

Results of NAVIGATOR (BLU-285-1101, NCT02508532)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
30-month OS KM estimate	N/A	N/A	N/A								
36-month OS KM estimate	Avapritinib	38	71.0 (55.9, 86.2)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
42-month OS KM estimate	Avapritinib	38	63.1 (43.3, 83.0)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
Median PFS	Avapritinib	38	24.0 (18.4 - -) months	N/A	N/A	N/A	N/A	N/A	N/A	PFS is defined as the time in months from the start of treatment to the date of first documented disease progression or death due to any cause, whichever occurs first. If a patient has not had an event, PFS is censored at the date of last valid assessment that is stable or better. Confidence intervals are calculated using the linear transformation.	
	N/A	N/A	N/A								
6-month PFS KM estimate	Avapritinib	38	94.3 (86.6, 100.0)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
12-month PFS KM estimate	Avapritinib	38	82.9 (70.4, 95.3)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								

Results of NAVIGATOR (BLU-285-1101, NCT02508532)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
18-month PFS KM estimate	Avapritinib	38	68.6 (53.2, 84.0)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
24-month PFS KM estimate	Avapritinib	38	53.4 (36.6, 70.2)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
30-month PFS KM estimate	Avapritinib	38	42.7 (23.2, 62.3)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
36-month PFS KM estimate	Avapritinib	38	34.2 (12.5, 55.8)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
Radiographic tumour reductions	Avapritinib	38	94.7% (- - -)	N/A	N/A	N/A	N/A	N/A	N/A	Radiographic tumour reductions assessed by central radiology using mRECIST Version 1.1.	
	N/A	N/A	N/A								

Table 59 Results per study for unresectable or metastatic GIST patients with PDGFRA D842V mutation; NAVIGATOR; avapritinib all doses

Results of NAVIGATOR (BLU-285-1101, NCT02508532)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
ORR	Avapritinib	56	91.1% (80.4–97.0)	N/A	N/A	N/A	N/A	N/A	N/A	Best response assessed by central radiology using mRECIST Version 1.1. The proportion of patients with a confirmed best response of CR or PR.	
	N/A	N/A	N/A								
CR	Avapritinib	56	12.5% (N/A)	N/A	N/A	N/A	N/A	N/A	N/A	Best response assessed by central radiology using mRECIST Version 1.1.	
	N/A	N/A	N/A								
PR	Avapritinib	56	78.6% (N/A)	N/A	N/A	N/A	N/A	N/A	N/A	Best response assessed by central radiology using mRECIST Version 1.1.	
	N/A	N/A	N/A								
SD	Avapritinib	56	8.9% (N/A)	N/A	N/A	N/A	N/A	N/A	N/A	Best response assessed by central radiology using mRECIST Version 1.1.	
	N/A	N/A	N/A								
PD	Avapritinib	56	0% (0.0)	N/A	N/A	N/A	N/A	N/A	N/A	Best response assessed by central radiology using mRECIST Version 1.1.	
	N/A	N/A	N/A								

Results of NAVIGATOR (BLU-285-1101, NCT02508532)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
CBR	Avapritinib	56	98.2% (90.4–100.0)	N/A	N/A	N/A	N/A	N/A	N/A	Best response assessed by central radiology using mRECIST Version 1.1. Two-sided 95% CI based on exact binomial distribution using the Clopper–Pearson method. The proportion of patients with confirmed CR/PR or SD lasting ≥4 cycles from first dose date.	
	N/A	N/A	N/A								
DCR	Avapritinib	56	100.0% (93.6–100.0)	N/A	N/A	N/A	N/A	N/A	N/A	Best response assessed by central radiology using mRECIST Version 1.1. The proportion of patients with a confirmed best response of CR, PR, or SD.	
	N/A	N/A	N/A								
Median DOR	Avapritinib	51	27.3 (17.6–32.2) months	N/A	N/A	N/A	N/A	N/A	N/A	Duration of response by central radiology per mRECIST 1.1 and EMA Censoring Rule.	
	N/A	N/A	N/A								

Results of NAVIGATOR (BLU-285-1101, NCT02508532)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
3-month DOR	Avapritinib	51	98.0 (94.1, 100.0)	N/A	N/A	N/A	N/A	N/A	N/A	Duration of Response is defined as the time in months from first documented response (CR/PR) to the date of first documented disease progression or death due to any cause, whichever comes first. Patients without confirmed CR or PR will be excluded from this analysis. Patients who are still in response at time of data cutoff will be censored at their last valid assessment. Confidence intervals are calculated using the linear transformation.	
	N/A	N/A	N/A								
6-month DOR	Avapritinib	51	86.0 (76.4, 95.6)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
9-month DOR	Avapritinib	51	81.8 (71.0, 92.6)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
12-month DOR	Avapritinib	51	73.3 (60.8, 85.8)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
18-month DOR	Avapritinib	51	61.9 (48.0, 75.9)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
24-month DOR	Avapritinib	51	51.3 (36.3, 66.3)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								

Results of NAVIGATOR (BLU-285-1101, NCT02508532)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
30-month DOR	Avapritinib	51	37.3 (19.9, 54.6)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
36-month DOR	Avapritinib	51	29.8 (10.8, 48.9)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
Median Time to first response (Range)	Avapritinib	51	61.0 (52-757)	N/A	N/A	N/A	N/A	N/A	N/A	Time to response is defined as the time in days from the start of treatment to the time the response criteria for CR or PR are first met per mRECIST Version 1.1. Patients without confirmed CR or PR will be excluded from this analysis.	
	N/A	N/A	N/A								
Median OS	Avapritinib	56	Not reached	N/A	N/A	N/A	N/A	N/A	N/A	OS was defined as the time from the start of treatment to the date of death. All patients who did not have a death record prior to or on the cut-off date were censored at either the data cut-off date or	
	N/A	N/A	N/A								
6-month OS KM estimate	Avapritinib	56	100.0 (100.0, 100.0)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								

Results of NAVIGATOR (BLU-285-1101, NCT02508532)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
12-month OS KM estimate	Avapritinib	56	92.5 (85.3, 99.6)	N/A	N/A	N/A	N/A	N/A	N/A	the last date known alive + 1, whichever occurred earlier. Kaplan–Meier estimates with censoring at the earlier of the data cut-off date and the last date known alive + 1. Progression-free survival per EMA censoring rule	
	N/A	N/A	N/A								
18-month OS KM estimate	Avapritinib	56	88.7 (80.1, 97.2)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
24-month OS KM estimate	Avapritinib	56	75.3 (63.6, 87.0)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
30-month OS KM estimate	Avapritinib	56	69.0 (56.4, 81.7)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
36-month OS KM estimate	Avapritinib	56	65.8 (52.1, 79.4)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
42-month OS KM estimate	Avapritinib	56	62.1 (47.5, 76.7)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								

Results of NAVIGATOR (BLU-285-1101, NCT02508532)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median PFS	Avapritinib	56	29.2 (22.9,-)months	N/A	N/A	N/A	N/A	N/A	N/A	PFS is defined as the time in months from the start of treatment to the date of first documented disease progression or death due to any cause, whichever occurs first. If a patient has not had an event, PFS is censored at the date of last valid assessment that is stable or better. Confidence intervals are calculated using the linear transformation.	
	N/A	N/A	N/A								
6-month PFS KM estimate	Avapritinib	56	92.5 (85.3, 99.6)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
12-month PFS KM estimate	Avapritinib	56	83.0 (72.9, 93.1)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
18-month PFS KM estimate	Avapritinib	56	71.7 (59.6, 83.8)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
24-month PFS KM estimate	Avapritinib	56	61.5 (48.2, 74.8)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
30-month PFS KM estimate	Avapritinib	56	45.4 (29.6, 61.1)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								

Results of NAVIGATOR (BLU-285-1101, NCT02508532)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
36-month PFS KM estimate	Avapritinib	56	37.2 (20.6, 53.8)	N/A	N/A	N/A	N/A	N/A	N/A		
	N/A	N/A	N/A								
Radiographic tumour reductions	Avapritinib	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Radiographic tumour reductions assessed by central radiology using mRECIST Version 1.1.	
	N/A	N/A	N/A								

Appendix C. Comparative analysis of efficacy

The main result of the indirect comparison is presented in Section 7.

C.1.1 Summary of trials used for the indirect comparison

As described in Appendix H, 44 publications were identified in the clinical SLR, of which 24 unique studies that specifically included GIST patients harbouring the PDGFRA D842V mutation.

Most of the studies identified by the clinical SLR contained limited information on patient characteristics, particularly around the lack of clarity on whether the populations were strictly unresectable or metastatic—a key driver of treatment outcomes—with some studies specifically including patients with localised disease (92). This makes comparison with these studies impossible, because resectable GIST has a completely different treatment pathway, surgical resection. As this is undertaken with curative intent, the treatment pathway results in a completely different prognosis. This is clearly inappropriate, as it would not be a like-for-like comparison with the population for which avapritinib is indicated.

The most relevant study to inform on the comparative efficacy of avapritinib from the NAVIGATOR trial is the BLU-285-1002 trial as it most closely resembles the patients seen in the NAVIGATOR trial and baseline characteristics were available to the authors to perform the analysis (5).

The full data set of the single-arm NAVIGATOR study provided clinical information on 56 patients diagnosed with unresectable or metastatic GIST harbouring a PDGFRA D842V mutation. These patients were treated with avapritinib. Some of them had previously been treated with one or more currently available TKIs: imatinib, sunitinib and regorafenib. The data cut used for this analysis was the March 2020 data cut. According to the protocol of the trial all patients (100%) had a confirmed diagnosis of unresectable GIST at the screening visit. At that time most patients (96.4%) also had metastatic disease.

The full data set of the natural history study BLU-285-1002 was also available. In this study, outcomes were measured in 22 advanced PDGFRA D842V GIST patients, treated with currently available TKI therapy. BLU-285-1002 was a multicentre, retrospective, observational study using data from clinical charts to characterize the natural history of disease in patients with PDGFRA D842V mutant GIST. According to the protocol of the study, patients with GIST harbouring a PDGFRA D842V mutation in the PDGFRA gene and treated with a kinase inhibitor for locally advanced, metastatic, or recurrent GIST, were included in the study.

For the interest of the current indirect comparison analysis, two groups can be defined, the first composed of 56 patients treated with avapritinib (cases group) from the

NAVIGATOR study, the second composed of 22 patients treated with other TKIs (controls group) from BLU-285-1002.

Cassier et al. was the only other study which provided PFS and OS outcomes, however baseline characteristics of the PDGFRA D842V subpopulation was not available (3). Cassier et al. is therefore used in a naïve comparison against the results of the IPW analysis to address any uncertainties that may arise from the IPW analysis.

C.1.2 Methods and outcomes of studies used in the indirect comparison

The primary endpoint of the analysis was (OS measured from the start of reference treatment to the date of death event (or censoring date). The secondary endpoint of the analysis was PFS measured from start of reference treatment to the date of progression event (or censoring date). Please note that within this definition of secondary endpoint, death was considered a censoring event. Progression was defined per RECIST criteria, in line with the protocol of the NAVIGATOR study.

In the NAVIGATOR study patients with a histologically or cytologically-confirmed diagnosis of unresectable or metastatic GIST were included and treated with avapritinib. BLU-285-1002 included patients treated with a kinase inhibitor for locally advanced, metastatic, or recurrent GIST. Therefore, while avapritinib was always used to treat unresectable or metastatic disease, this was not necessarily the case with the first TKI used in BLU-285-1002. As a result, it was not appropriate to compare the outcomes from the first TKI in BLU-285-1002 with avapritinib in the NAVIGATOR study, as unresectable or metastatic disease is a key prognostic factor. For this reason, a review of the medical history for all 22 patients in BLU-285-1002 was conducted, with the specific objective of identifying the first TKI used to treat unresectable or metastatic disease. In most cases the first TKI for unresectable or metastatic disease was not the first TKI that patients had received in BLU-285-1002, meaning that the patient received previous lines as adjuvant therapy. The most appropriate comparison for avapritinib in the NAVIGATOR study compared to ECM in BLU-285-1002 was therefore conducted using data from the first TKI for unresectable or metastatic disease in BLU-285-1002.

Therefore, for both OS and PFS analyses the reference treatment was defined as follows:

- NAVIGATOR study → reference treatment = avapritinib treatment
- BLU-285-1002 → reference treatment = first tyrosine kinase inhibitor (TKI) for treatment of unresectable or metastatic GIST

C.1.3 Methods of analysis of studies included in the indirect or mixed treatment comparison

C.1.3.1 Confounding factors

Based on the scientific literature and the comparable variables available for both studies, some factors potentially associated with treatment outcomes were identified. The distribution of these factors in the case and control group was analysed in terms of absolute numbers and relative frequencies (percentages) and it was compared using the

Chi-Square Test and the standard difference (SD) (both weighted and unweighted) based on the prevalence between groups (67, 68).

Table 60 summarizes the confounding factors used in the analysis. Age, metastatic disease and Eastern Cooperative Oncology Group (ECOG) performance status were estimated at the start of the reference treatment, while the anatomical site of the primary tumour was recorded at the primary diagnosis. The duration of the disease was estimated from the date of diagnosis to the date the reference treatment was started. The number of TKIs was counted from the first TKI for treatment of unresectable or metastatic disease.

Table 60 Confounding factors

Parameter	Catergorisation
Sex	Male/Female
Age	< 60 y/≥ 60 y
Race	White/Non white
Anatomical site of primary tumour	Gastric/Small bowel or rectal
Metastatic disease	Yes/No
ECOG performance status	0 / 1 / 2+
Duration of disease	< 3 y/≥ 3 y
Number of total TKIs* (including avapritinib)	1 / 2 / 3 / 4+

Abbreviations: ECOG = Eastern Cooperative Oncology Group; TKI = tyrosine kinase inhibitor.

Notes: *, counting from the first TKI for treatment of unresectable or metastatic disease.

The first TKI for treatment of unresectable or metastatic disease was identified by manual scrutiny of patients' listing in BLU-285-1002 and of patients' clinical history in the NAVIGATOR study.

C.1.3.2 Survival analysis

The number of patients included in the analysis was 56 for the NAVIGATOR study and 19 for BLU-285-1002. Three patients from BLU-285-1002 were not included, as they did not receive TKI treatment for unresectable or metastatic GIST. All three patients received just one single TKI (imatinib) and this was used in adjuvant setting.

Survival analysis was performed on the two groups to evaluate the effectiveness of treatment with avapritinib. The Kaplan–Meier method was used to obtain survival curves from the observed time to event.

The comparison between the two survival curves was done using the statistical hypothesis log-rank test, to test the null hypothesis that there is no difference between the population survival curves. Under the null hypothesis, the risk of death (number of deaths/number alive) was calculated from the combined data for both groups. The survival functions were also compared in terms of the fraction of patients alive at various time points (6, 12, 18 and 24 months).

The propensity score (PS) method was used to adjust for imbalances in the characteristics of the two groups of patients. Considering the low number of patients, the PS weighting method was preferred to PS matching. A multivariate logistic regression model was used to generate the PS indicating the probability of being assigned to cases rather than controls. All the available covariates were included in this model, following the recommendations on PS analysis. Weights calculated were used to estimate IPW survival functions, to repeat the comparison between the NAVIGATOR study and BLU-285-1002 after adjusting for confounding factors.

All analyses were carried out using STATA software (Version 13.0).

C.1.4 Unadjusted survival functions for BLU-285-1002 compared to the NAVIGATOR study

C.1.4.1 Unadjusted overall survival

The proportion of patients alive at 6, 12, 18 and 24 months is reported in Table 61. Figure 24 presents the unadjusted Kaplan–Meier survival functions for OS in the NAVIGATOR study and in BLU-285-1002. The median survival in BLU-285-1002 is 26.4 months, while it is not reached in the NAVIGATOR study.

Table 61 Unadjusted Kaplan–Meier survival estimates of overall survival at key time points in the NAVIGATOR study (avapritinib) and BLU-285-1002 (standard TKI therapy)

Kaplan-Meier survival estimates	NAVIGATOR	BLU-285-1002
Median, months	Not reached	26.4
6-months	100%	84.2%
12-months	92.5%	79.0%
18-months	88.7%	68.4%
24-months	75.3%	63.2%

Abbreviations: TKI = tyrosine kinase inhibitors

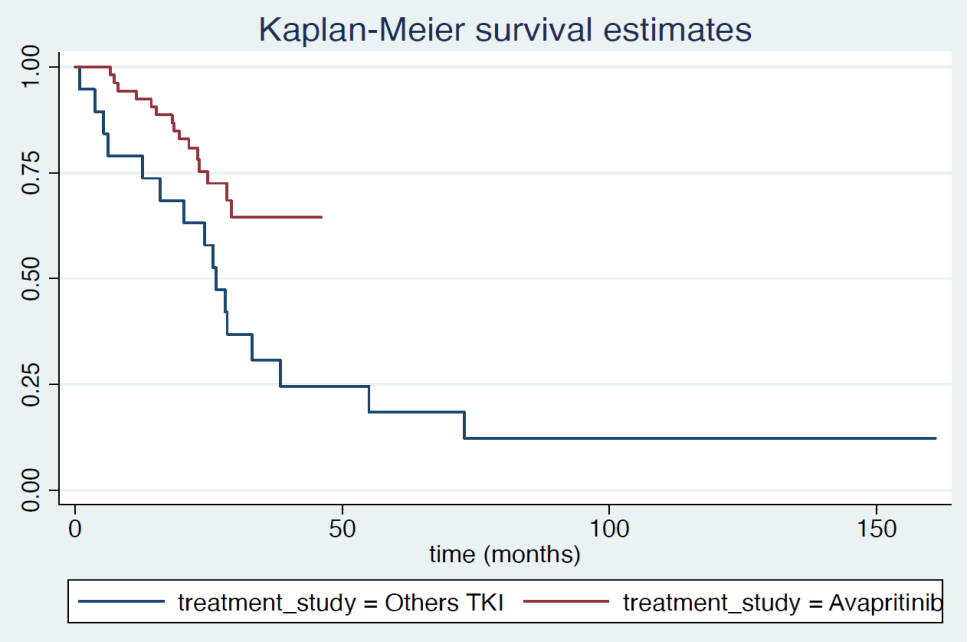

Figure 24 Unadjusted Kaplan–Meier curves for overall survival in the NAVIGATOR study (avapritinib) and BLU-285-1002 (standard TKI therapy)

Abbreviations: TKI = tyrosine kinase inhibitors

The two survival curves were compared using the statistical hypothesis log-rank test, to test the null hypothesis that there is no difference between the population survival curves. Under the null hypothesis, we calculate the risk of death (number of deaths/number alive) from the combined data for both groups. The log-rank test is significant, so we reject the null hypothesis, and can say that the differences observed in the two survival curves are not due to chance. Table 62 presents the results of the log-rank test.

Table 62 Log-rank test for equality of survivor functions (overall survival)

Treatment	Events observed	Event observed
Other TKIs	16	9.77
Avapritinib	15	21.23
Total	31	31.0
	$X^2 = 6.92$	
	$Pr > chi^2 = 0.0085$	

Abbreviations: X2 = chi squared; TKI = tyrosine kinase inhibitor

C.1.4.2 Unadjusted progression-free survival

The proportion of patients alive and progression-free at 6, 12, 18 and 24 months is reported in Table 63. Figure 25 presents the unadjusted Kaplan–Meier survival functions for PFS in the NAVIGATOR study and BLU-285-1002. The median PFS in BLU-285-1002 is 3.4 months, while it is not reached in the NAVIGATOR study.

Table 63 Unadjusted Kaplan–Meier survival estimates of progression-free survival at key time points in the NAVIGATOR study (avapritinib) and BLU-285-1002 (standard TKI therapy)

Kaplan-Meier survival estimates	NAVIGATOR	BLU-285-1002
Median, months	Not reached	3.4
6-months	92.5%	13.6%
12-months	86.6%	6.8%
18-months	76.6%	6.8%
24-months	76.6%	6.8%

Abbreviations: TKI = tyrosine kinase inhibitors

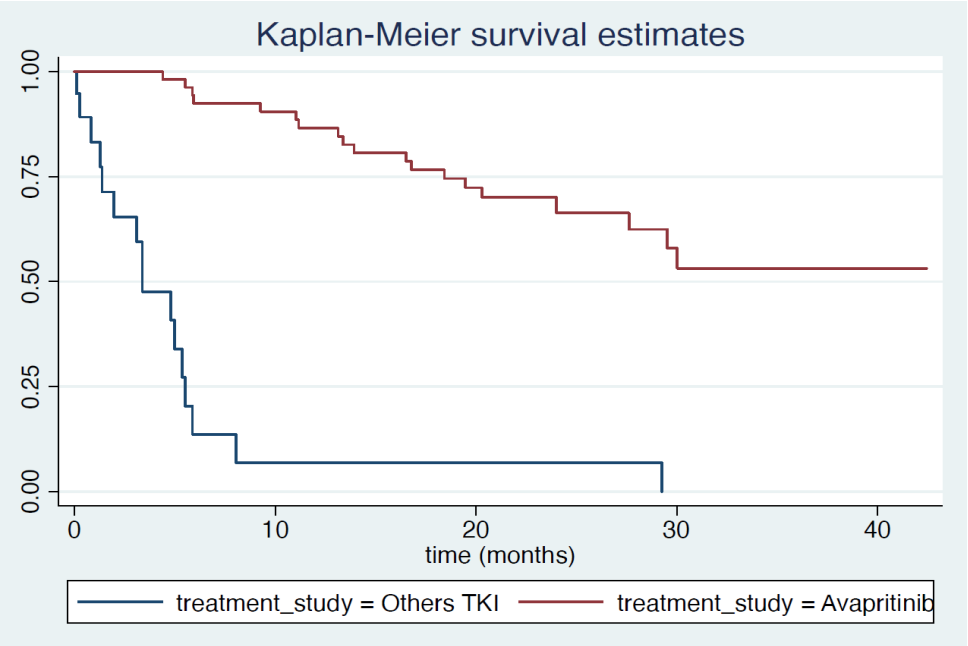

Figure 25 Unadjusted Kaplan–Meier curves for progression-free survival in the NAVIGATOR study (avapritinib) and BLU-285-1002 (standard TKI therapy)

Abbreviations: X2 = chi squared; TKI = tyrosine kinase inhibitor

The comparison between the two survival curves was performed using the statistical hypothesis log-rank test, to test the null hypothesis that there is no difference between the population survival curves. Under the null hypothesis, the risk of death (number of deaths/number alive) from the combined data for both groups was calculated. The log-rank test was significant, so the null hypothesis was rejected, and we can say that the

differences observed in the 2 survival curves are not due to chance. The log-rank test results are presented in Table 64.

Table 64 Log-rank test for equality of survivor functions (progression-free survival)

Treatment	Events observed	Event observed
Other TKIs	16	2.94
Avapritinib	19	32.06
Total	35	35.0
Chi^2 (1) = 69.17		
Pr > chi^2 = 0.0000		

C.1.5 IPTW distribution

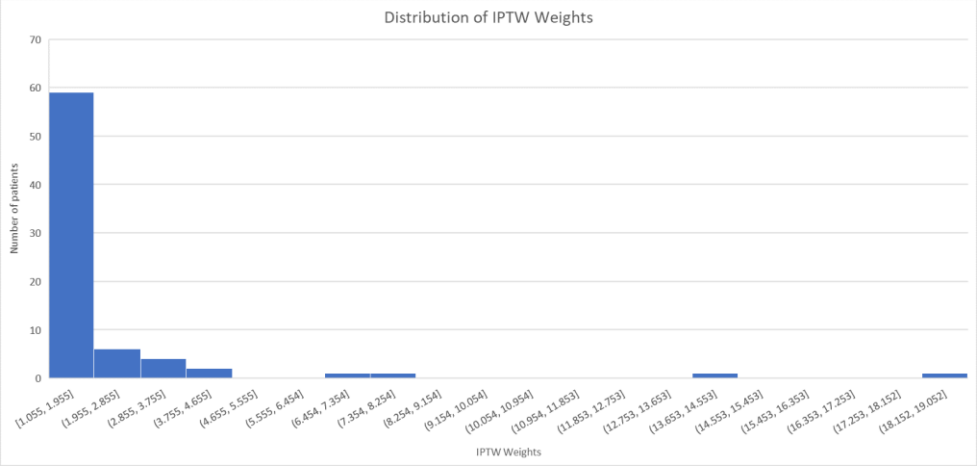

Figure 26 IPTW distribution

C.1.6 Uncertainties in the indirect and mixed treatment comparison

There is some uncertainty in the generalisability of the mix of treatments used in BLU-285-1002 to the treatment pathway used in clinical practice in Europe. At first line in BLU-285-1002, 47.4% of patients were treated with imatinib, 42.1% were treated with sunitinib, 5.3% were treated with regorafenib, and 5.3% of patients were treated with crenolanib (5). As BLU-285-1002 was based in the US, it is not surprising that there are some treatment differences compared to ECM in Europe. Furthermore, the limited use of regorafenib was likely due to the recruitment dates of the study, when regorafenib was not widely available.

The extent of this uncertainty is limited by the fact that the most commonly used treatments throughout BLU-285-1002 are imatinib and sunitinib, which is broadly in line with the GIST treatment pathway confirmed by UK clinical experts (30). Furthermore, existing TKIs are expected to have limited efficacy for patients with the PDGFRA D842V

mutation (30, 34), so treatment outcomes would be expected to be similar regardless of the treatment that was used. The other treatments used were mainly investigational products used in clinical trials or compassionate use programs, or treatments used off label. It is therefore possible that the use of some of the investigational products in BLU-285-1002 may bias these data in favour of the comparator.

Finally, the face validity of the results are supported by the similarity in outcomes between the weighted analysis of BLU-285-1002 and the Cassier et al. 2012 study (3), which was confirmed by UK clinicians to be the most appropriate publicly available source of evidence for a naïve comparison to the NAVIGATOR study. The UK clinicians also agreed that Cassier et al. 2012 was reflective of the outcomes they would expect to see for these patients in clinical practice (30). Figure 27 presents a comparison of the Kaplan–Meier curves for PFS and OS outcomes in these two studies. The similarity of these curves supports both the assumption that these patients with the PDGFRA D842V mutation would be expected to have minimal benefit from current therapy—regardless of the treatment used—and the use of the weighted BLU-285-1002 data as the most appropriate source of comparator data for the NAVIGATOR study.

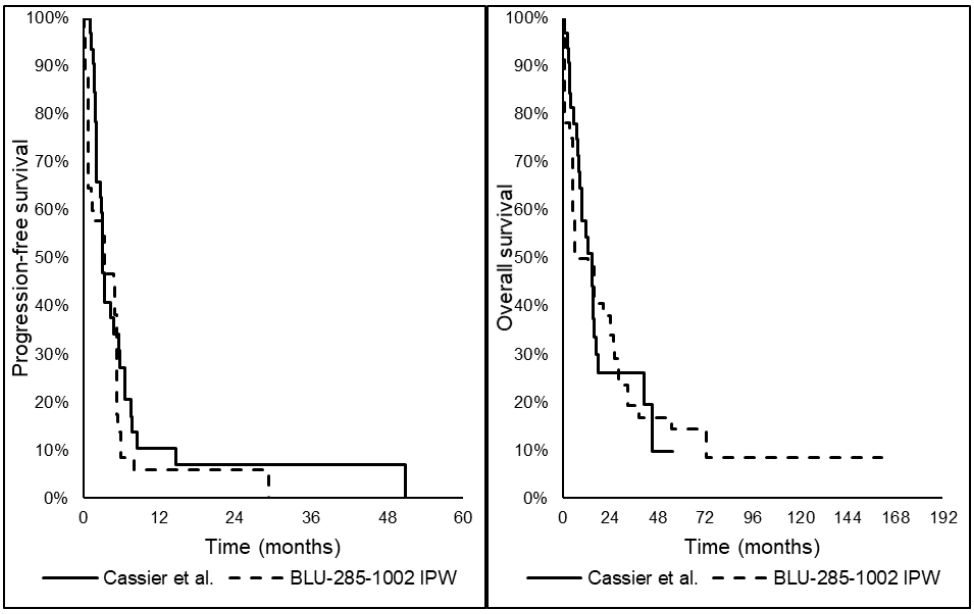

Figure 27 Comparison of PFS and OS Kaplan-Meier curves, IPW-adjusted BLU-285-1002 and Cassier et al.

Abbreviations: IPW = inverse probability weighting; OS = overall survival; PFS = progression-free survival; TKI = tyrosine kinase inhibitor.

Source: Weighted comparison of BLU-285-1002 and the NAVIGATOR study (5)

Appendix D. Extrapolation

This appendix specifies the extrapolation of the endpoints: OS, PFS, and ToT for both the avapritinib and ECM treatment arm. OS, PFS and ToT use the datasets from NAVIGATOR IPW for avapritinib and BLU-285-1002 for ECM.

D.1 Extrapolation of overall survival

D.1.1 Data input

Avapritinib

Overall survival in the avapritinib arm was captured and extrapolated based on the information available from the NAVIGATOR (data cut-off: March 2020). The base case uses the IPW NAVIGATOR data sets and BLU-285-1002 data sets. Given that NAVIGATOR is a single-arm trial, the best available evidence of OS for patients not receiving avapritinib is provided via the IPW BLU-285-1002 data. Consequently, the estimate of avapritinib OS can be achieved through combination of NAVIGATOR OS data censoring for discontinuation events (to capture mortality of patients still receiving avapritinib), OS analysis of ECM patients via IPW BLU-285-1002 (to capture survival of patients not receiving avapritinib), and ToT analysis from NAVIGATOR.

Figure 28 and Figure 29 show both the unadjusted and the IPW adjusted KM data, demonstrating that IPW had no discernible effect on the original KM data from the NAVIGATOR study.

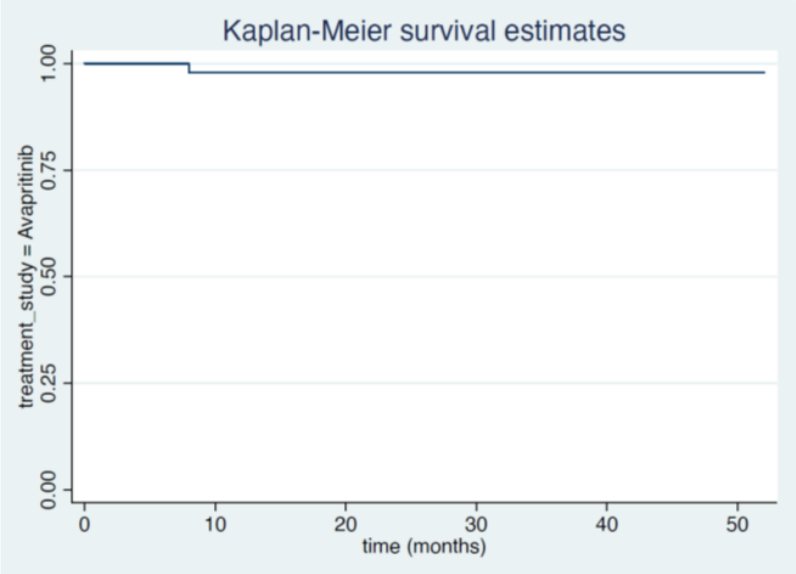

Figure 28 Kaplan-Meier curve for avapritinib – unadjusted (censored for discontinuation)

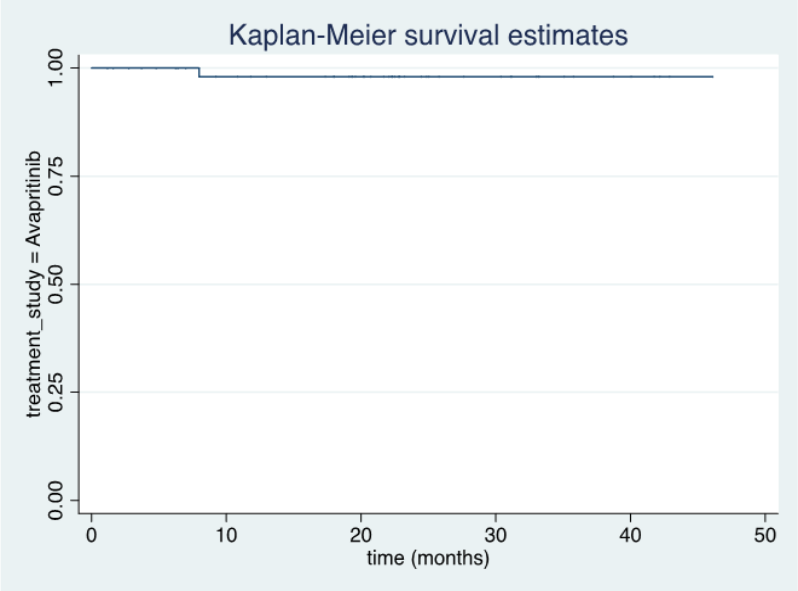

Figure 29 Kaplan-Meier curve for avapritinib - IPW adjusted (censored for discontinuation)

ECM

The IPW analysis of the BLU-285-1002 appears to provide the most suitable ECM survival data. The KM data from BLU-285-1002 is shown in Figure 30.

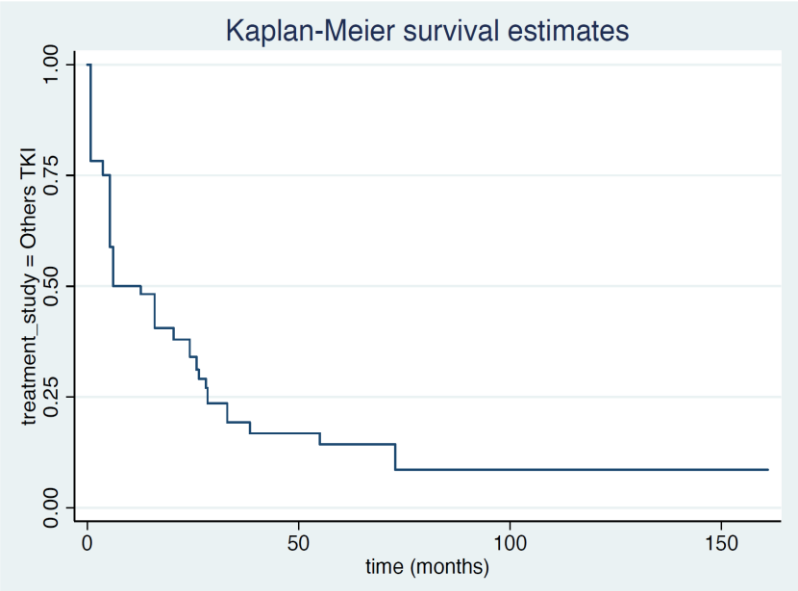

Figure 30 Kaplan-Meier curve for ECM - BLU-285-1002, IPW adjusted

D.1.2 Model

Extrapolation of OS was generated by fitting parametric models to the Kaplan-Meier curves from the IPW data from the NAVIGATOR study (data cut-off: March 2020) or from

BLU-285-1002. Five parametric distributions were fitted to the study data: Exponential, Weibull, Gompertz, Log-normal, and Log-logistic.

Based on the OS data derived from the NAVIGATOR study and BLU-285-1002, separate individual parametric models were chosen for the avapritinib arm and ECM arm. The Log-normal parametric model was selected to model the OS in the avapritinib arm, while the Weibull parametric model was chosen for the ECM arm.

Avapritinib

Given the low number of events in the Kaplan–Meier data, it is difficult to evaluate the fit of the parametric models. Figure 31 shows the extrapolation model of OS for avapritinib. Figure 32 shows the extrapolation model (OS) over the time horizon (40 years).

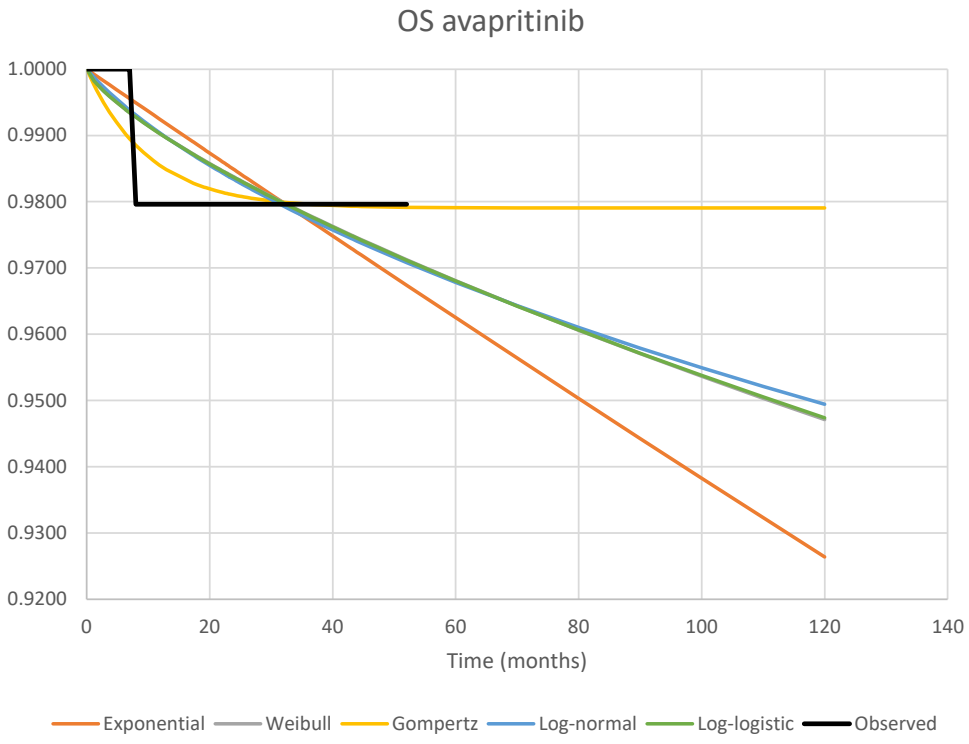

Figure 31 OS extrapolation model, avapritinib, IPW adjusted (censored for discontinuation)

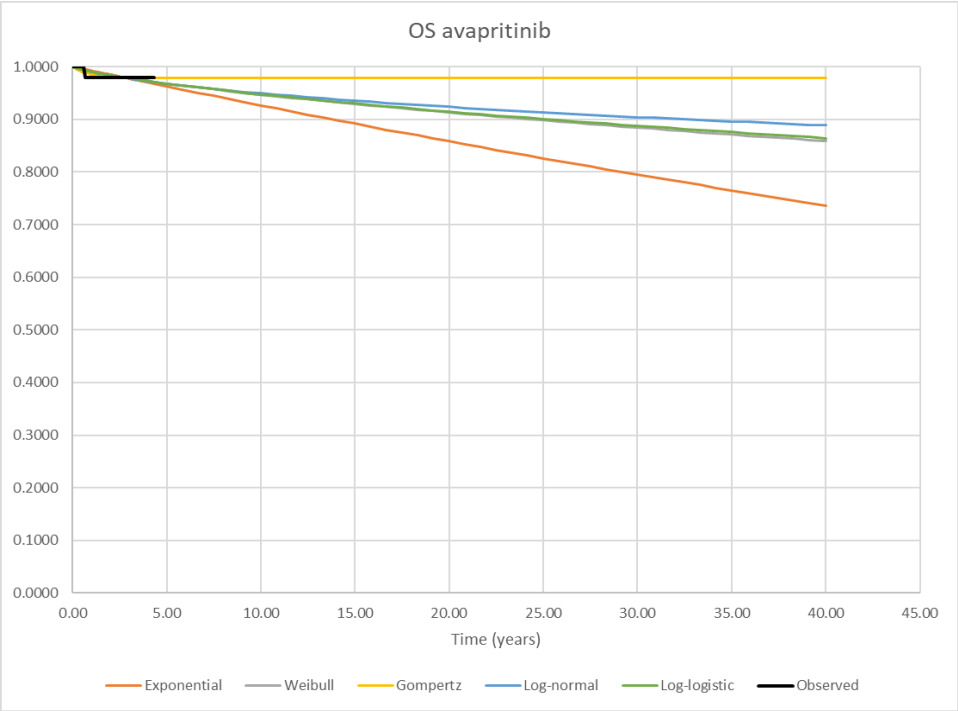

Figure 32 OS extrapolation model, avapritinib, IPW adjusted (censored for discontinuation), 40 years

Table 65 presents the OS estimates over time for avapritinib.

Table 65 OS estimates at set time points – avapritinib IPW weighted data

Time point	Avapritinib				
	Exponential	Weibull	Gompertz	Log-normal	Log-logistic
0 months	100.0%	100.0%	100.0%	100.0%	100.0%
10 months	99.3%	99.1%	98.7%	99.2%	99.1%
20 months	98.6%	98.5%	98.2%	98.4%	98.5%
40 months	97.1%	97.3%	97.9%	97.3%	97.3%
60 months	95.7%	96.3%	97.8%	96.3%	96.3%
80 months	94.3%	95.3%	97.8%	95.4%	95.3%
100 months	93.0%	94.4%	97.8%	94.7%	94.4%
120 months	91.6%	93.5%	97.8%	94.0%	93.5%

ECM

Figure 33 shows the parametric model fits to the observed data from the IPW BLU-285-1002 data. Figure 33 shows the long-term model extrapolations.

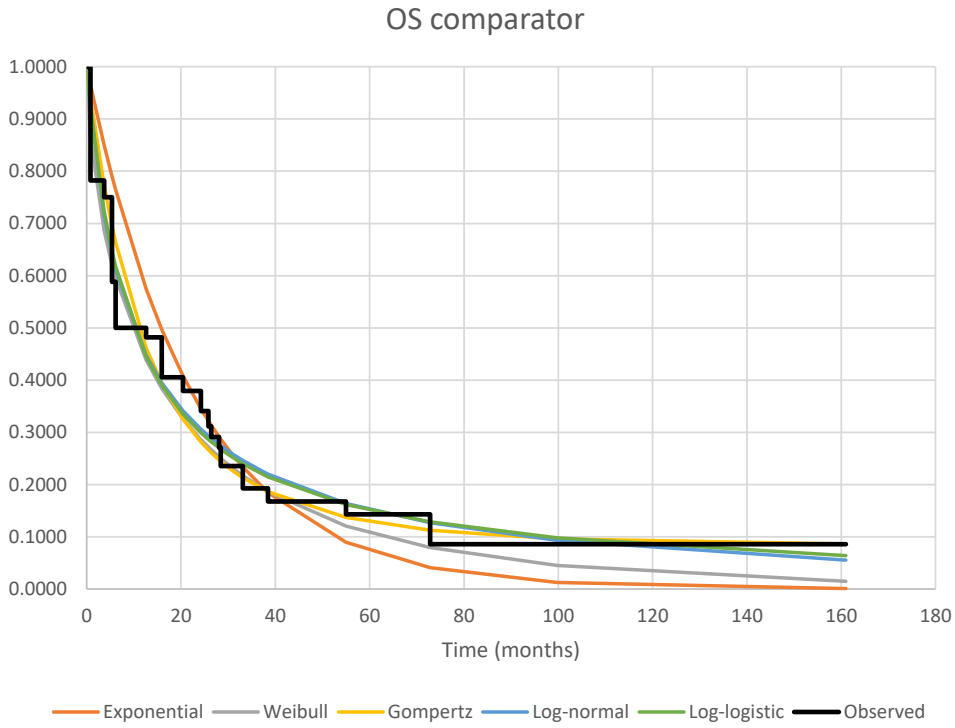

Figure 33 OS extrapolation model during study follow-up—ECM, IPW BLU-285-1002

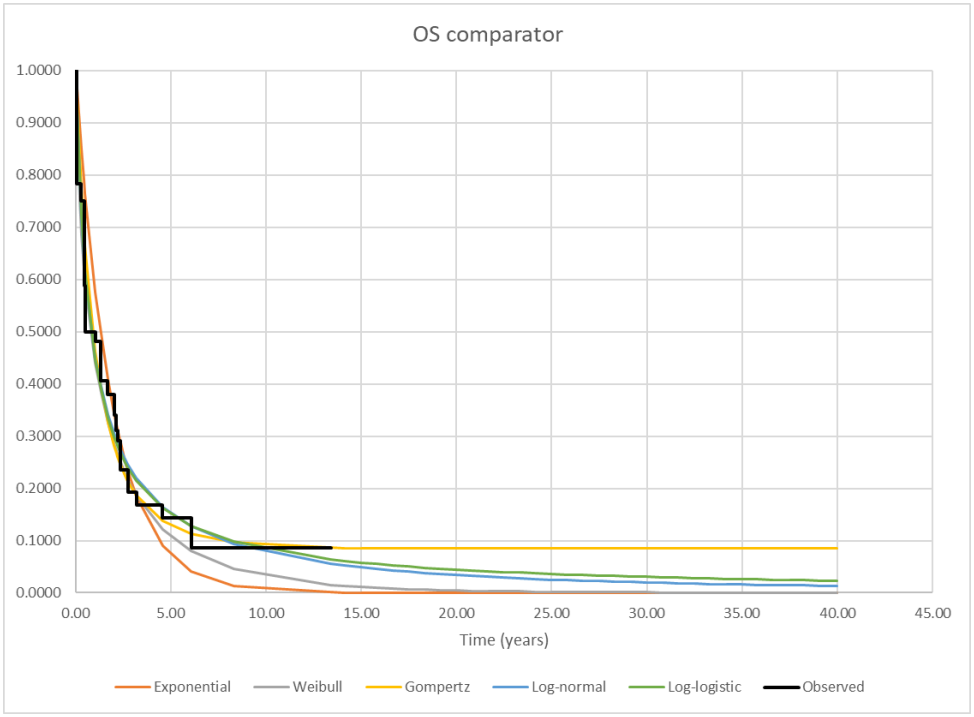

Figure 34 OS extrapolation model during study follow-up—ECM, IPW BLU-285-1002, 40 years

Table 66 presents the OS estimates over time for ECM.

Table 66 OS estimates at set time points – ECM, IPW adjusted data

Time point	Avapritinib				
	Exponential	Weibull	Gompertz	Log-normal	Log-logistic
0 months	100.0%	100.0%	100.0%	100.0%	100.0%
10 months	64.5%	49.2%	53.0%	50.1%	50.1%
20 months	41.6%	33.1%	33.1%	34.6%	34.0%
40 months	17.3%	17.8%	18.0%	21.3%	20.8%
60 months	7.2%	10.7%	12.8%	15.2%	15.1%
80 months	3.0%	6.8%	10.7%	11.6%	11.9%
100 months	1.2%	4.5%	9.6%	9.3%	9.8%
120 months	0.5%	3.1%	9.1%	7.7%	8.3%

It is acknowledged that according to the NICE TSD 14, it is advisable to use the same type of model for consistency in cases where parametric models are fitted separately to

individual treatment arms. For the extrapolation of OS, the Log-normal model was chosen for the avapritinib arm, while the Weibull model was chosen for the ECM arm. This decision was made based on clinical validation, which confirmed that these respective distributions align well with the observed survival patterns in each arm. According to the NICE TSD 14, distinct parametric functions are justifiable when clinical plausibility or evidence can be justified, requiring specific parametric models for accurate representation. To ensure result robustness and evaluate alternative modeling approaches, sensitivity analyses were performed and Weibull model was explored for OS in the avapritinib arm as well.

D.1.3 Proportional hazards

The assumption of proportional hazards should be tested, indicating whether it is preferable to fit separate parametric models to each treatment arm or allow for time-varying hazard ratios. However, according to the NICE TSD 14, when IPD are available, it is unnecessary to rely upon the proportional hazards assumption and apply a proportional hazards modelling approach. Fitting separate parametric models to each treatment arm involves fewer assumptions, although it does also require the estimation of more parameters.

Additionally, Schoenfeld tests and log-cumulative hazard plots were conducted to assess the proportional hazards assumption. However, if the proportional hazards assumption did not hold, it was deemed inappropriate to apply a proportional hazards modeling approach. This further justifies the choice to option for separate single fits, as it allows for more flexibility in capturing time-varying effects and accommodating potential deviations from the proportional hazards assumption.

Therefore, in the comparative analysis utilizing an ITC approach to compare avapritinib with ECM, separate single fits were chosen for the two treatment arms. This decision was based on the need to account for distinct treatment effects, the use of IPW adjusted data to address confounding, and the lack of proportional hazards assumption. These considerations ensure a more accurate representation of the survival outcomes and enhance the reliability of the comparative analysis.

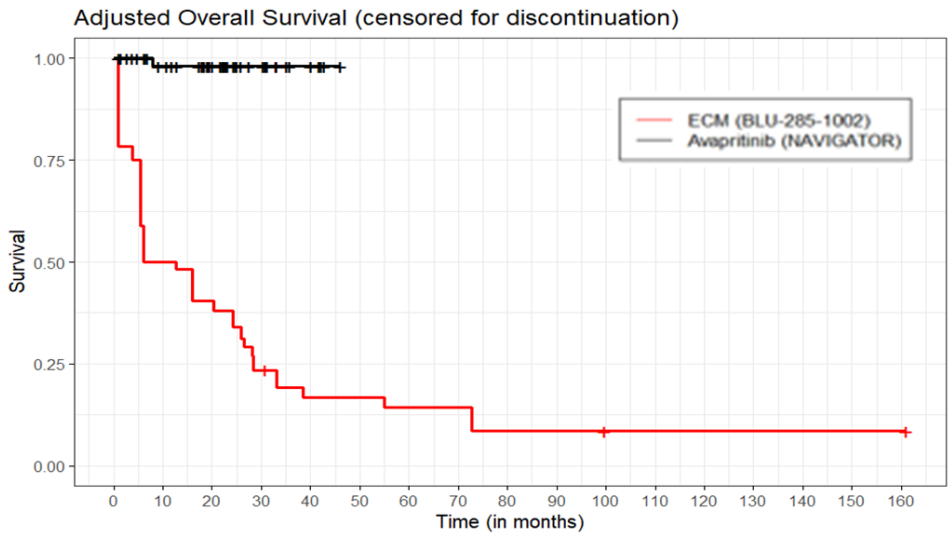

Figure 35 Overall survival KM for avapritinib vs ECM, IPW adjusted (censored for discontinuation).

The log-cumulative hazard plot for avapritinib vs ECM is shown in Figure 36. The Schoenfeld plot for avapritinib vs ECM is shown in Figure 37.

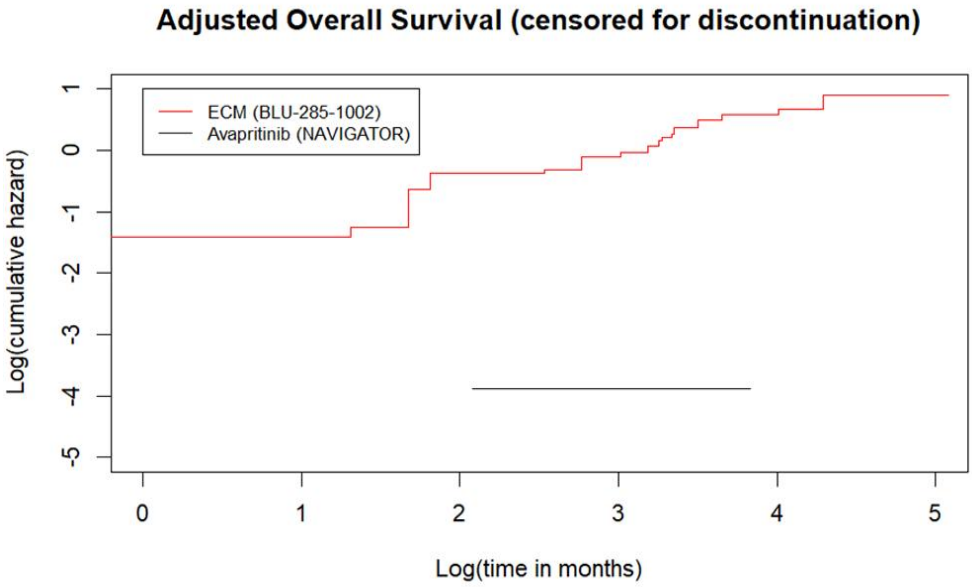

Figure 36 Log-cumulative hazard plot OS – avapritinib vs ECM, IPW adjusted, censored for discontinuation.

As Figure 36 illustrates, the log-cumulative hazard plots indicates that the proportional hazard assumption is violated.

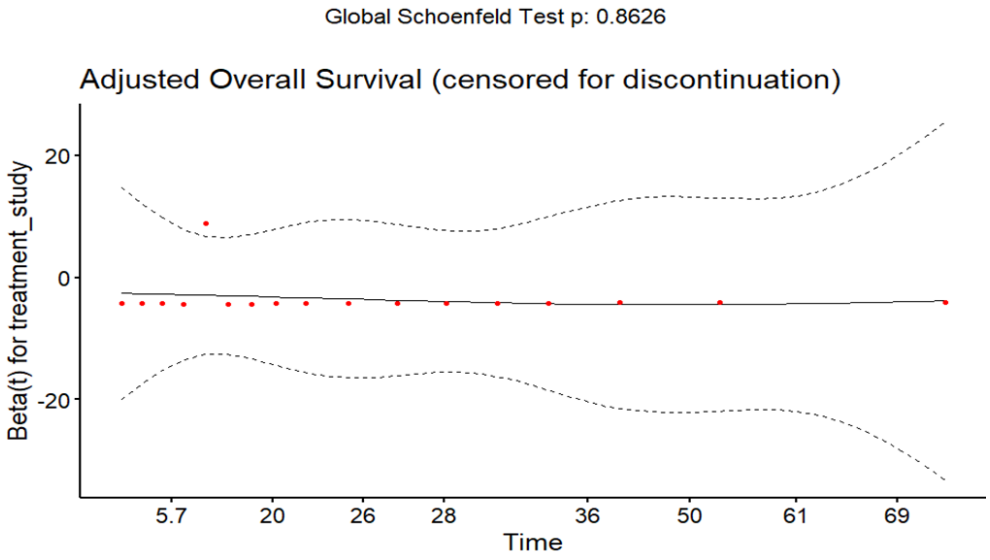

Figure 37 Schoenfeld plot OS - avapritinib vs ECM, IPW adjusted, censored for discontinuation.

While the Schoenfeld test for the PH assumption may not indicate a violation, other considerations may still warrant the use of separate fits to ensure an accurate and comprehensive analysis of the survival outcomes.

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

Table 67 presents the statistical fit of each OS parametric model for both avapritinib and ECM.

Table 67 OS statistical fit, AIC and BIC

Model	Avapritinib		ECM	
	AIC	BIC	AIC	BIC
Exponential	18.39	20.41	373.12	374.06
Weibull	20.24	24.29	343.73	345.62
Gompertz	20.66	24.71	571.38	573.27
Log-normal	21.36	25.41	567.17	569.06
Log-logistic	21.54	25.59	570.05	571.94

Avapritinib

The Exponential model produces the best statistical fit; however, the visual inspection is poor. The second-best statistical fit is the Weibull model. However, the Weibull model provides a pessimistic extrapolation of OS along with Gompertz. Clinical plausibility must

be taken into consideration when selecting the most appropriate model, and the Log-normal model provide a middle ground whilst having a very similar visual fit to the KM data to the Weibull model.

ECM

The Weibull model has the best statistical fit according to both the AIC and BIC statistics.

D.1.5 Evaluation of visual fit

Avapritinib

Refer to Figure 31. Choosing Log-normal for extrapolation generates a realistic and clinical plausible result, considering the expected hazard profile and statistical fit. As the individual observations are weighted in the IPW analysis, AIC and BIC are less reliable. Greater consideration should therefore be given to the visual fits and clinical plausibility of the curves when selecting the best extrapolation for use in the model.

The Log-normal model was used in the base case as the visual fit of all extrapolations is quite similar. The clinical expert supported the final model estimates produced using Log-normal extrapolation.

ECM

Refer to Figure 33. The curves generally fit well with the Kaplan-Meier data, but they start to underestimate survival as the number of patients at risk decreases towards the tail end. The Gompertz model, however, shows a different pattern, with survival reaching a plateau at around 100 months, refer to Table 66, The Exponential model, on the other hand, has the weakest visual fit overall, overestimating survival until approximately 20 months yet underestimating survival from 40 months onwards.

D.1.6 Evaluation of hazard functions

Smoothed hazard plots for avapritinib and ECM are shown in Figure 38 and Figure 39 , respectively.

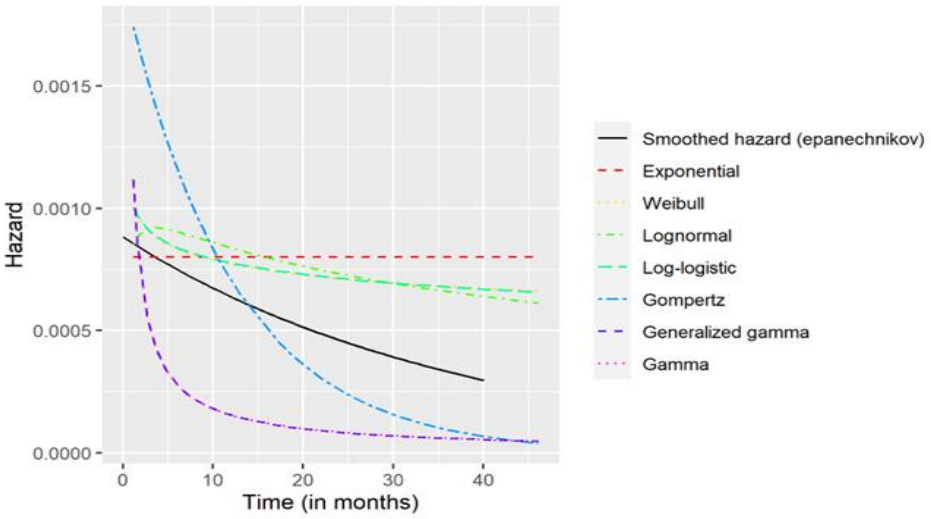

Figure 38 Smoothed hazard plots for OS - avapritinib, IPW adjusted (censored for discontinuation)

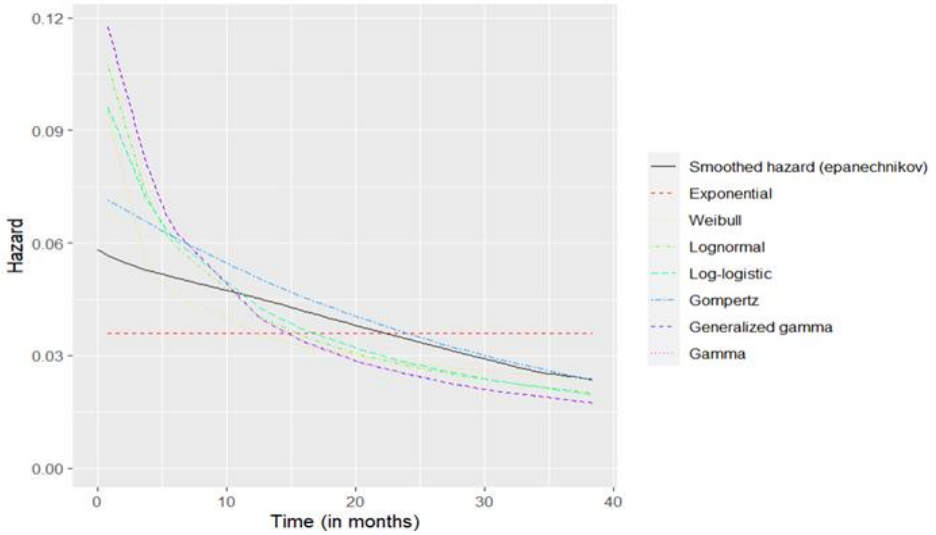

Figure 39 Smoothed hazard plots for OS - ECM, IPW adjusted (censored for discontinuation)

For avapritinib, the Weibull, Log-normal, Log-logistic, Gompertz, Generalized Gamma and Gamma model all generated decreasing hazard profiles, with the Generalized Gamma, Gamma and Gompertz generating a slightly sharper decrease compared to the other parametric models. Lastly, the Exponential model generated a constant risk of mortality over time.

For ECM, the Weibull, Log-normal, Log-logistic, Gompertz, Generalized Gamma and Gamma model also all generated slightly decreasing hazard profiles. Again, the Exponential model generated a more constant hazard profile.

However, it is important to note that the appropriateness of the hazard profiles produced by each parametric model for each treatment arm requires clinical expert feedback.

Adjustment of background mortality

Throughout the model, the mortality rate is set to be at least that of the age- and sex-adjusted general population in Denmark.

D.1.7 Adjustment for treatment switching/cross-over

Not applicable.

D.1.8 Waning effect

To account for the gradual loss of treatment effect upon discontinuation of avapritinib, the model incorporates a gradual transition of the OS hazard from the avapritinib arm to the ECM arm. In the base case analysis, we assumed this effect to disappear gradually over 12 months. This was in accordance with Danish market research (38) and supported by a German clinical expert (63).

The model link ToT to OS by using a "tunnel state" approach lasting for 12 cycles, the model calculates per-cycle probability of death based on time since discontinuation, capturing the gradual loss of avapritinib treatment effect on OS. The simple linear interpolation is between the per-cycle death probabilities associated with the avapritinib and ECM arm extrapolations of OS Kaplan–Meier data. This approach addresses uncertainties in immature OS data and provides more flexibility than a simple extrapolation. It aligns with clinical expert input and evidence of gradual decline in survival benefit after discontinuation (38, 52) .

D.1.9 Cure-point

Not applicable.

D.1.10 Validation and discussion of extrapolated curves

The survival estimates produced by the final base case model were presented to a clinical expert. The clinical expert indicated that the PFS and OS estimates produced by the model are clinically plausible, given the disease-modifying effect of avapritinib for eligible patients (52).

A limitation of linking ToT to OS using censoring rules is that it adds complexity to the cost-effectiveness model through the introduction of a tunnel state. However, doing so allows us to model the clinical and economic impacts of scenarios affecting ToT and the benefit of avapritinib beyond treatment. As the mortality of discontinued patients gradually approaches the mortality of the control arm, the impact of any factor affecting ToT is reflected in the estimation of OS, providing the best possible assessment of their worth in practice. Failing to do this would contradict clinical expert opinion, as we were advised that the benefits of treatment would be lost gradually.

D.2 Extrapolation of progression-free survival

D.2.1 Data input

Avapritinib

The PFS data was captured and extrapolated based on the IPW NAVIGATOR data (data cut-off: March 2020). Figure 40 and Figure 41 show both the unadjusted and the IPW adjusted KM data (censored for death).

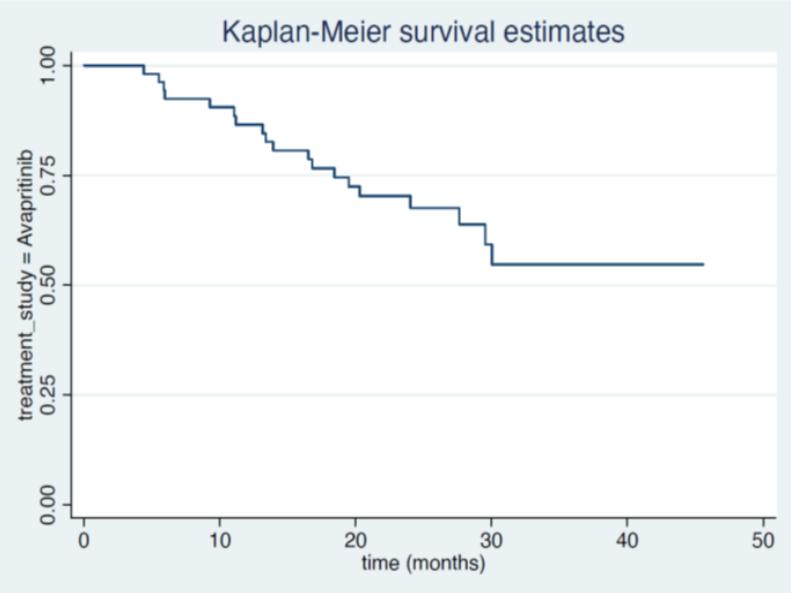

Figure 40 Kaplan-Meier curve of PFS, avapritinib, censoring for death, unadjusted

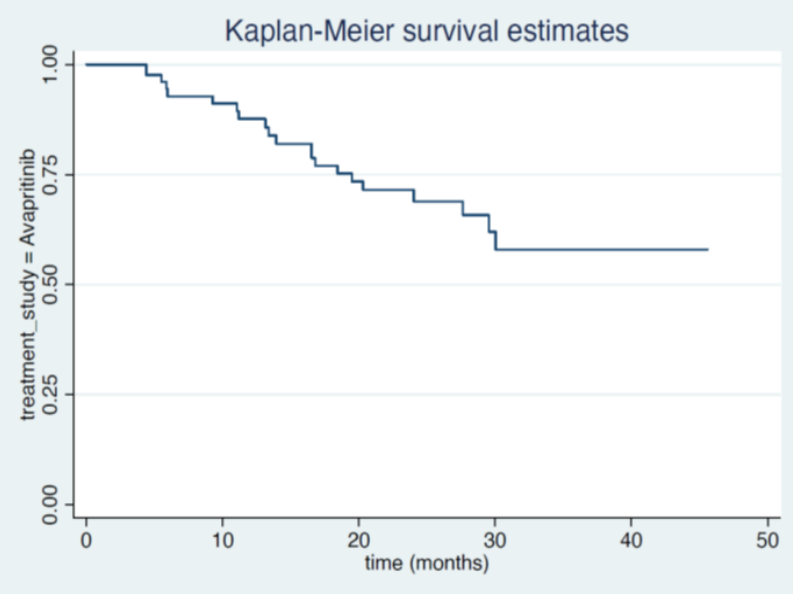

Figure 41 Kaplan-Meier curve of PFS, avapritinib, censoring for death, IPW adjusted

ECM

For the sequence of treatments in the ECM arm, the IPW BLU-285-1002 data were used as a source for PFS in the model base case, for the same reasons as those outlined for OS. Due to the availability of PLD it allows for censoring rules to be applied to isolate the estimated probability of individual events (e.g., of only progression) so that the assumption of equal subsequent progression rate across treatment arms can be applied. Figure 42 shows the IPW adjusted KM data from BLU-285-1002.

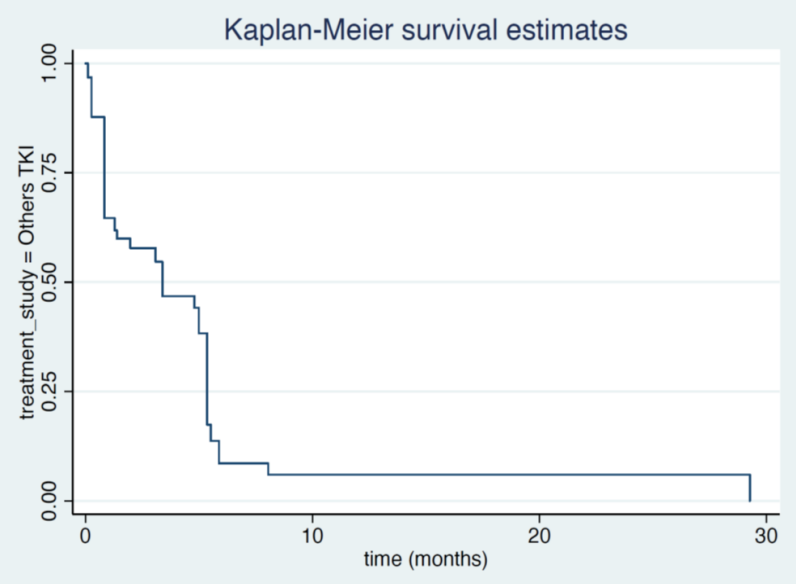

Figure 42 Kaplan-Meier curve of PFS, ECM, censoring for death, IPW adjusted

D.2.2 Model

Extrapolation of PFS was generated by fitting parametric models to the Kaplan-Meier curves from the IPW data from the NAVIGATOR study (data cut-off: March 2020) or from BLU-285-1002. Five parametric distributions were fitted to the study data: Exponential, Weibull, Gompertz, Log-normal, and Log-logistic.

Based on the PFS data derived from the NAVIGATOR study and BLU-285-1002, separate individual parametric models were chosen for the avapritinib arm and ECM arm. The Weibull parametric model was selected to model the PFS in both the avapritinib arm and the ECM arm.

Avapritinib

Figure 43 shows the extrapolation model of PFS for avapritinib. Figure 44 shows the extrapolation model (PFS) over the time horizon (40 years).

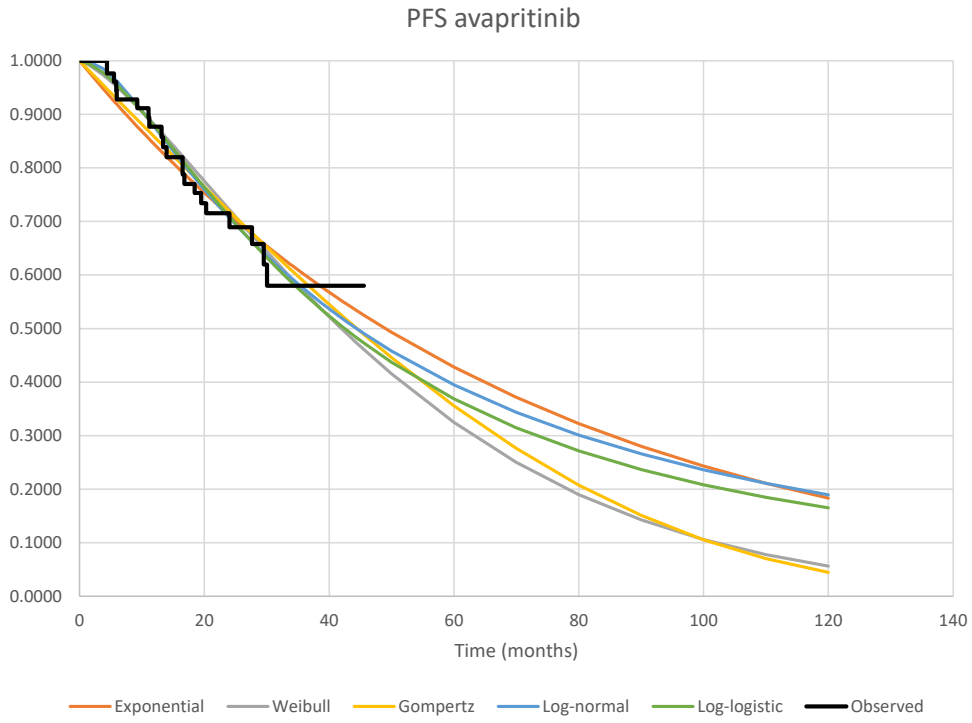

Figure 43 PFS extrapolation model, avapritinib, IPW adjusted (censored for death)

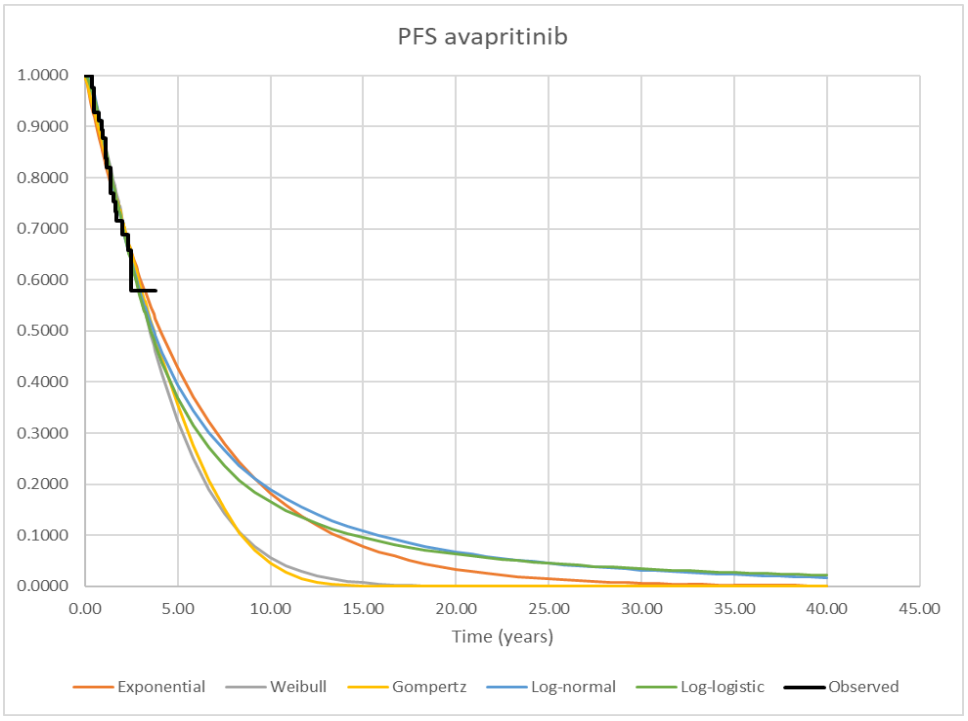

Figure 44 PFS extrapolation model, avapritinib, IPW adjusted (censored for death), 40 years

Table 68 presents the PFS estimates over time for avapritinib.

Table 68 PFS estimates at set time points – avapritinib IPW weighted data

Time point	Avapritinib				
	Exponential	Weibull	Gompertz	Log-normal	Log-logistic
0 months	100.0%	100.0%	100.0%	100.0%	100.0%
10 months	86.8%	90.5%	88.1%	90.6%	90.5%
20 months	75.4%	77.6%	76.5%	76.0%	76.4%
40 months	56.8%	52.2%	54.5%	53.7%	52.4%
60 months	42.8%	32.5%	35.6%	39.5%	36.9%
80 months	32.2%	19.0%	20.8%	30.1%	27.1%
100 months	24.3%	10.6%	10.5%	23.6%	20.8%
120 months	18.3%	5.6%	4.5%	19.0%	16.5%

ECM

Figure 45 show the extrapolation model of PFS for ECM. Figure 46 shows the extrapolation model (PFS) over the time horizon (40 years).

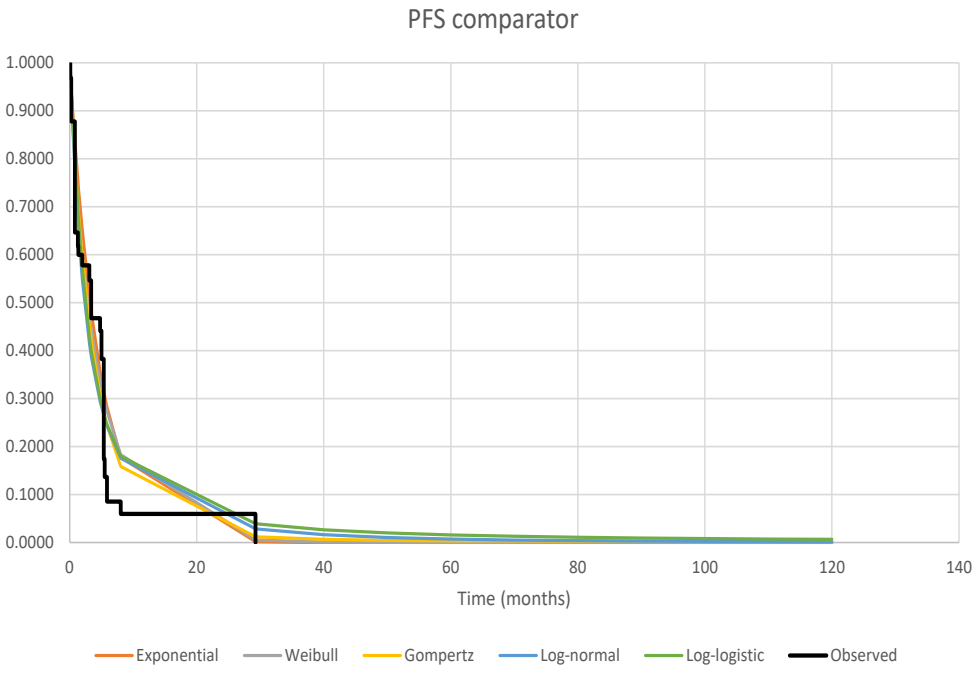

Figure 45 PFS models during trial follow-up, ECM, IPW-adjusted BLU-285-1002 (1L)

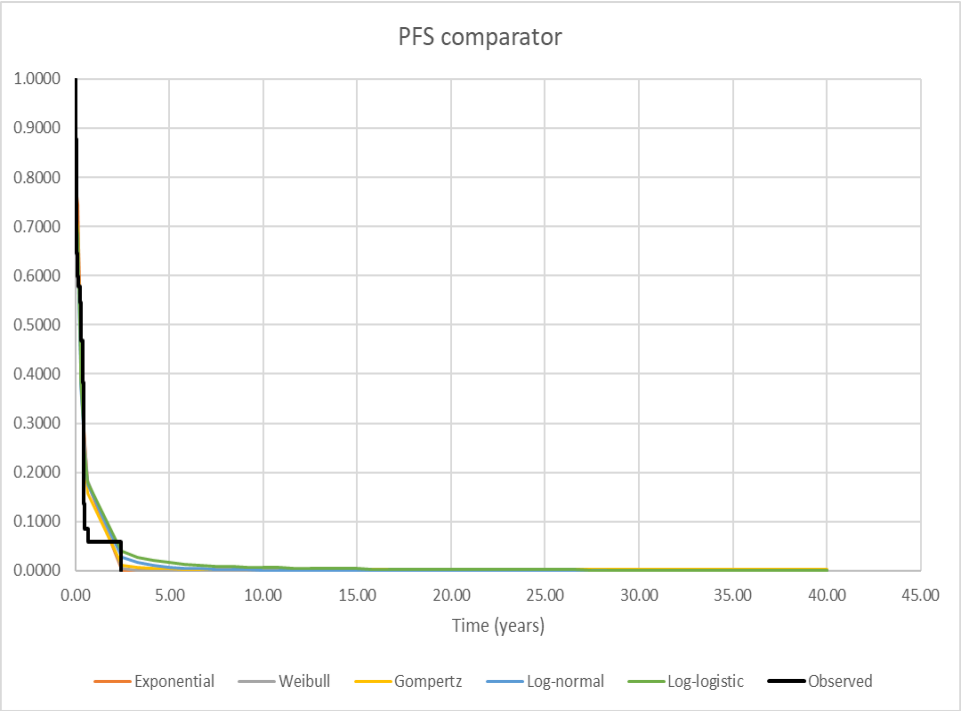

Figure 46 PFS models, ECM, IPW-adjusted BLU-285-1002 (1L), 40 years

Table 69 presents the PFS estimates over time for ECM.

Table 69 PFS estimates at set time points – ECM IPW weighted data

Time point	Avapritinib				
	Exponential	Weibull	Gompertz	Log-normal	Log-logistic
0 months	100.0%	100.0%	100.0%	100.0%	100.0%
10 months	11.7%	13.0%	11.2%	13.7%	14.2%
20 months	1.4%	2.5%	2.8%	5.4%	6.3%
40 months	0.0%	0.1%	0.7%	1.7%	2.7%
60 months	0.0%	0.0%	0.4%	0.8%	1.6%
80 months	0.0%	0.0%	0.3%	0.4%	1.1%
100 months	0.0%	0.0%	0.3%	0.2%	0.8%
120 months	0.0%	0.0%	0.3%	0.2%	0.7%

For the PFS analysis, both the avapritinib and ECM arm utilized the Weibull distribution for extrapolation, in line with NICE TSD 14, as mentioned in Appendix D.1.2. However, the

decision to use the Weibull distribution in both arms for PFS analysis does not undermine the validity or reliability of the previous section Appendix D.1.2 for OS, but reflects a specific modeling choice driven by the clinical nature of the PFS endpoint and considerations for comparability between treatments.

D.2.3 Proportional hazards

Same justification as described in Appendix D.1.3.

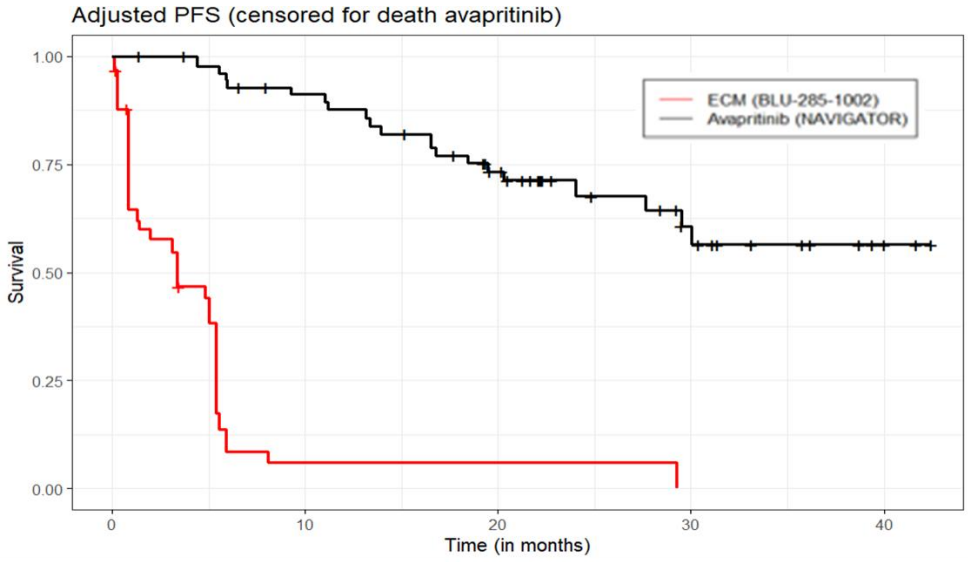

Figure 47 Progression free survival KM for avapritinib vs ECM, IPW adjusted (censored for death).

The log-cumulative hazard plot for avapritinib vs ECM is shown in Figure 48. The Schoenfeld plot for avapritinib vs ECM is shown in Figure 49.

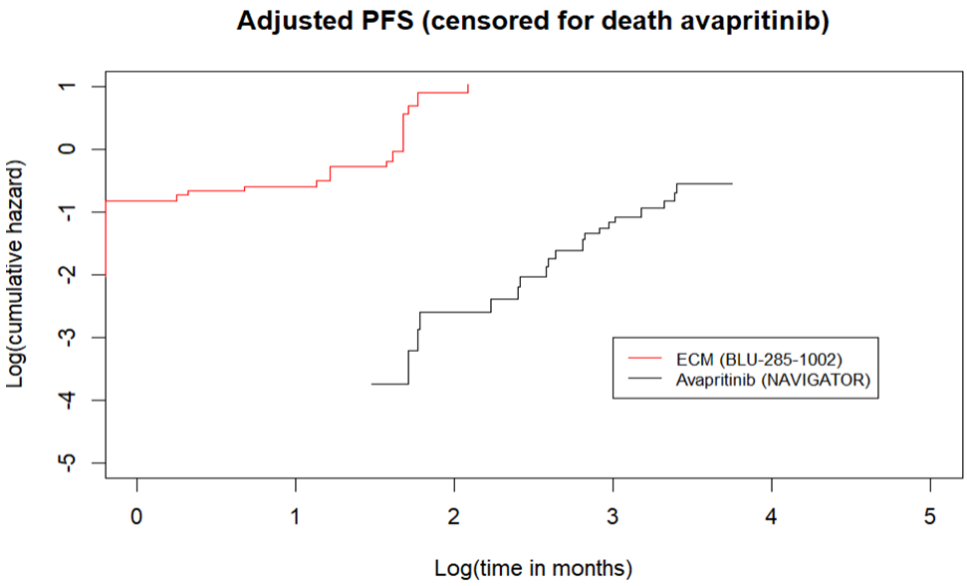

Figure 48 Log-cumulative hazard plot PFS – avapritinib vs ECM, IPW adjusted, censored for death.

As Figure 48illustrates, the log-cumulative hazard plots indicates that the proportional hazard assumption is violated.

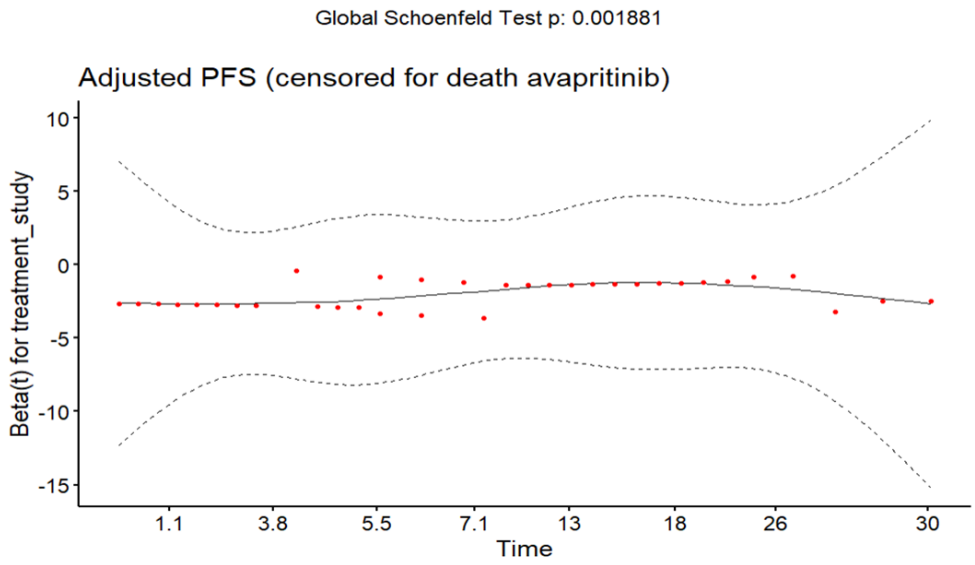

Figure 49 Schoenfeld plot PFS - avapritinib vs ECM, IPW adjusted, censored for death

Again, the Schoenfeld test for the PH assumption may not indicate a violation, however, other considerations may still warrant the use of separate fits to ensure an accurate and comprehensive analysis of the survival outcomes.

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

Table 70 presents the statistical fit of each PFS parametric model for both avapritinib and ECM.

Table 70 PFS statistical fit, AIC and BIC

Model	Avapritinib		ECM	
	AIC	BIC	AIC	BIC
Exponential	128.46	130.49	281.61	282.55
Weibull	127.98	132.03	279.67	281.56
Gompertz	159.89	163.94	360.63	362.52
Log-normal	154.66	158.71	361.54	363.43
Log-logistic	156.34	160.39	363.88	365.76

Avapritinib

Weibull and Exponential both showed reasonable statistical fits. With differences greater than 5 versus the distributions with the lowest AIC/BIC statistics (Weibull and Exponential), the Gompertz, Log-normal and Log-logistic models were considered to have the poorest statistical fit.

ECM

The Weibull and Exponential models had the lowest AIC and BIC values and were the only models to give AIC/BIC values within 5 of each other, which is often used as a rough guide for statistical equivalence. These two are therefore considered to have the best statistical fit.

D.2.5 Evaluation of visual fit

Avapritinib

Refer to Figure 43. Each model displays a similar fit with respect to the KM data. The Exponential model may be considered to underestimate the KM data until approximately 15 months. Both the Exponential and Weibull curves showed reasonable visual and statistical fits to the observed data. As the probability of progression is not expected to increase with time for patients treated with avapritinib, the Weibull model was used in the base case.

ECM

Refer to Figure 45. All models display similar visual fits to the KM data from IPW adjusted BLU-285-1002 during the follow-up period. The Weibull model was used in the base case as it had the best statistical fit as well as good visual fit to the clinical data.

D.2.6 Evaluation of hazard functions

Smoothed hazard plots for avapritinib and ECM are shown in Figure 50 and Figure 51, respectively.

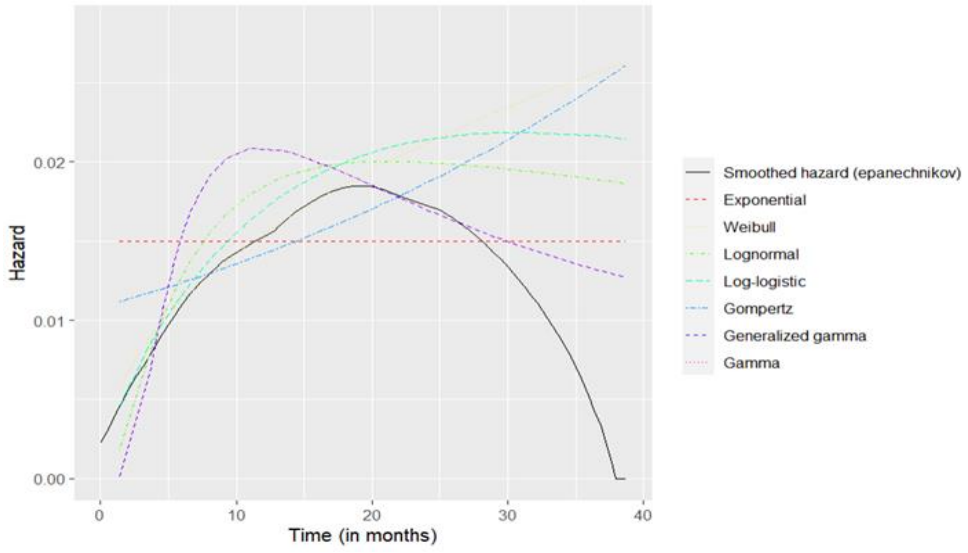

Figure 50 Smoothed hazard plots for PFS - avapritinib, IPW adjusted (censored for death)

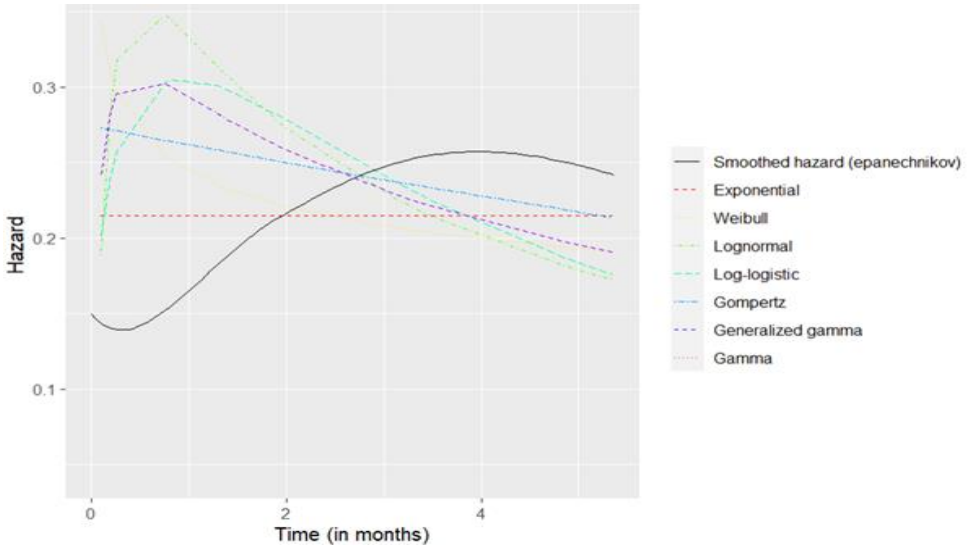

Figure 51 Smoothed hazard plots for PFS - avapritinib, IPW adjusted (censored for death)

For avapritinib, the Log-normal, Log-logistic, Generalized Gamma and Gamma model all generated increasing then decreasing hazard profiles, with Generalized Gamma and Gamma producing a slightly sharper short-term increase. The Gompertz and Weibull model produced a more steadily increasing risk of death over time. The Exponential model generated a constant risk of mortality over time.

For ECM, the Log-normal, Log-logistic, Generalized Gamma and Gamma model all generated increasing then decreasing hazard profiles, all with a slightly sharper short-term

increase followed by a sharp decline in hazards. The Weibull model produced a decreasing but linear hazard plot that appeared to flatten very slowly over time. The Gompertz model generated a continually increasing risk of deaths over time. Again, the Exponential model generated a more constant hazard profile.

D.2.7 Adjustment of background mortality

Throughout the model, the mortality rate is set to be at least that of the age- and sex-adjusted general population in Denmark (70).

D.2.8 Adjustment for treatment switching/cross-over

Not applicable.

D.2.9 Waning effect

Not applicable for PFS.

D.2.10 Cure-point

Not applicable.

D.2.11 Validation and discussion of extrapolated curves

The survival estimates produced by the final base case model were presented to a clinical expert. The clinical expert indicated that the PFS and OS estimates produced by the model are clinically plausible, given the disease-modifying effect of avapritinib for eligible patients (52).

D.3 Extrapolation of time on treatment

D.3.1 Data input

Avapritinib

ToT for avapritinib was captured and extrapolated based on IPW NAVIGATOR data. Figure 52 and Figure 53 show both the unadjusted and the IPW adjusted KM data.

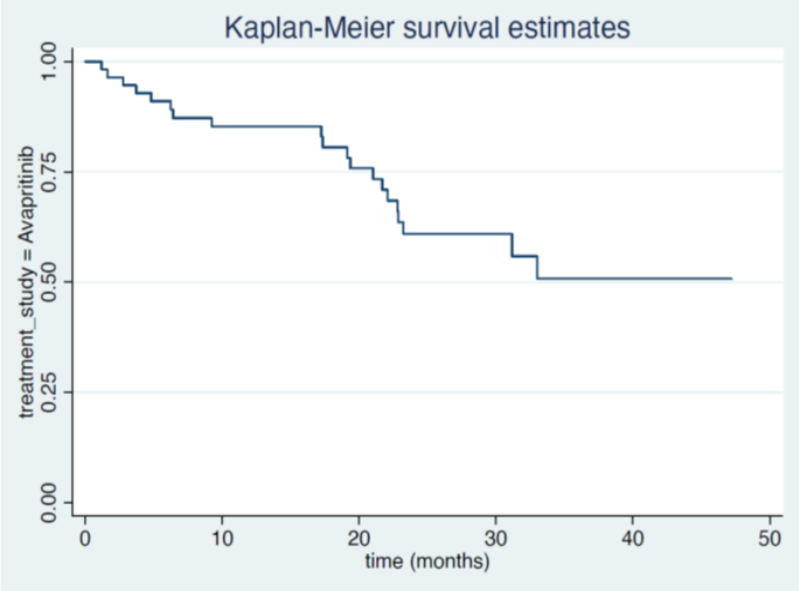

Figure 52 ToT Kaplan-Meier data, avapritinib, unadjusted

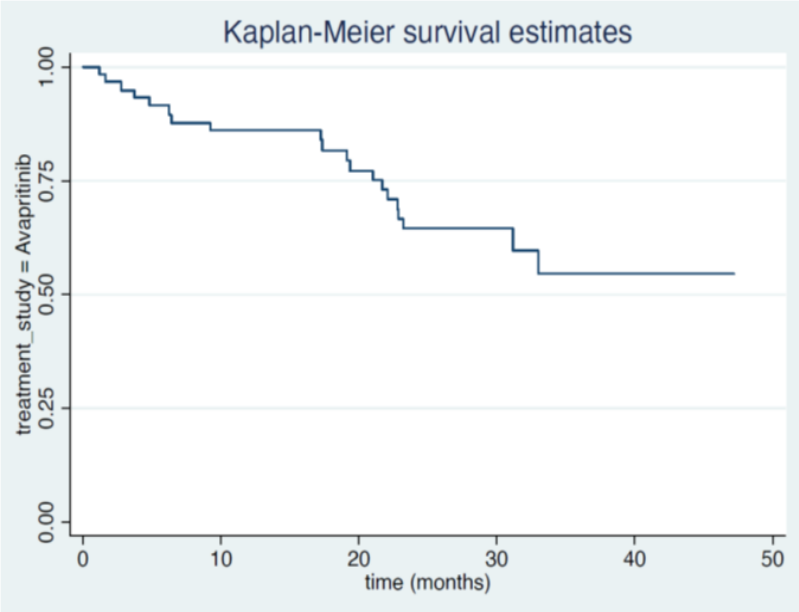

Figure 53 ToT Kaplan-Meier data, avapritinib, IPW adjusted

Five parametric distributions were fitted to the study data. Table 71 presents the ToT estimates over time for avapritinib.

Table 71 ToT estimates at set time points – avapritinib IPW weighted data

Time point	Avapritinib				
	Exponential	Weibull	Gompertz	Log-normal	Log-logistic
0 months	100.0%	100.0%	100.0%	100.0%	100.0%
10 months	86.0%	87.1%	87.0%	85.5%	86.9%
20 months	74.0%	74.5%	74.8%	72.9%	73.9%
40 months	54.7%	53.4%	53.3%	56.5%	54.9%
60 months	40.5%	37.7%	35.8%	46.2%	42.6%
80 months	29.9%	26.3%	22.6%	38.9%	34.3%
100 months	22.1%	18.2%	13.2%	33.6%	28.4%
120 months	16.4%	12.5%	7.0%	29.4%	24.1%

ECM

There was no data to inform time on treatment for ECM. For the ECM arm it is assumed that patients are treated until disease progression. ToT for ECM in the model is therefore using PFS as a proxy.

D.3.2 Model

Extrapolation of ToT was generated by fitting parametric models to the Kaplan-Meier curves from the IPW data from the NAVIGATOR study (data cut-off: March 2020). Five parametric distributions were fitted to the study data: Exponential, Weibull, Gompertz, Log-normal, and Log-logistic.

Based on the ToT data derived from the NAVIGATOR study, an individual parametric models were chosen for the avapritinib arm. The Gompertz parametric model was selected to model the ToT in the avapritinib arm.

Avapritinib

Figure 54 presents the extrapolation models to the IPW weighted KM data from the NAVIGATOR study. Figure 55 shows the extrapolation model (ToT) over the time horizon (40 years).

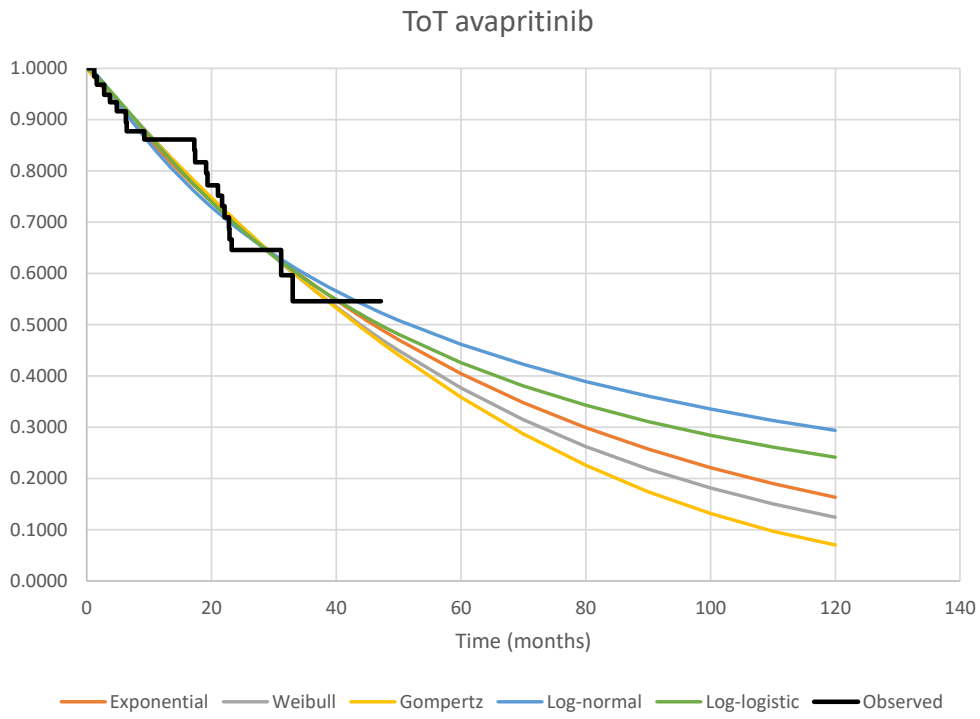

Figure 54 ToT models during trial follow-up, avapritinib, IPW adjusted (censored for death) data from NAVIGATOR

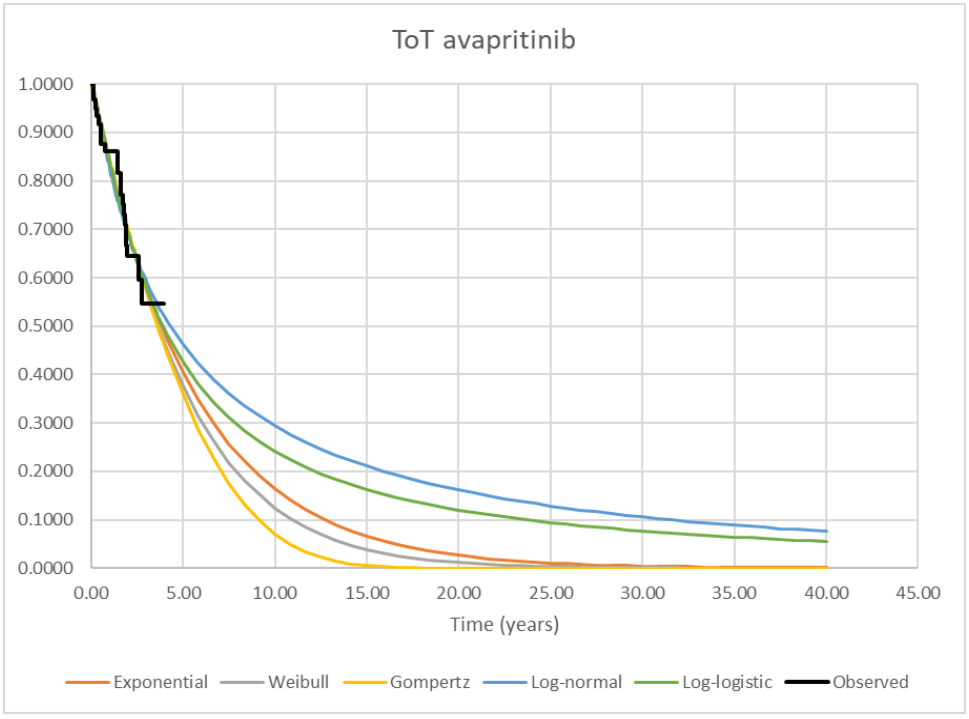

Figure 55 Extrapolation model for ToT, avapritinib, IPW adjusted (censored for death) data from NAVIGATOR - 40 years

D.3.3 Proportional hazards

Not applicable.

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

Table 72 presents the statistical fit of each ToT parametric model for avapritinib.

Table 72 ToT statistical fit, AIC and BIC

Model	Avapritinib	
	AIC	BIC
Exponential	140.02	142.04
Weibull	141.78	145.83
Gompertz	169.91	173.96
Log-normal	170.50	174.55
Log-logistic	170.05	174.10

Avapritinib

All models present reasonable fits to the observed data during the follow-up period. The Exponential and Weibull models had similar AIC and BIC values, indicating good statistical fit. However, the clinical expert preferred the Gompertz model due to its clinically plausible results.

D.3.5 Evaluation of visual fit

Avapritinib

Refer to Figure 54. All models present reasonable fits to the observed data during the follow-up period. The Exponential and Weibull models had similar AIC and BIC values, indicating good statistical fit. However, the clinical expert preferred the Gompertz model due to its clinically plausible results. Therefore, based on clinical plausibility, the Gompertz model was used in the base case.

D.3.6 Evaluation of hazard functions

Smoothed hazard plots for avapritinib shown in Figure 56.

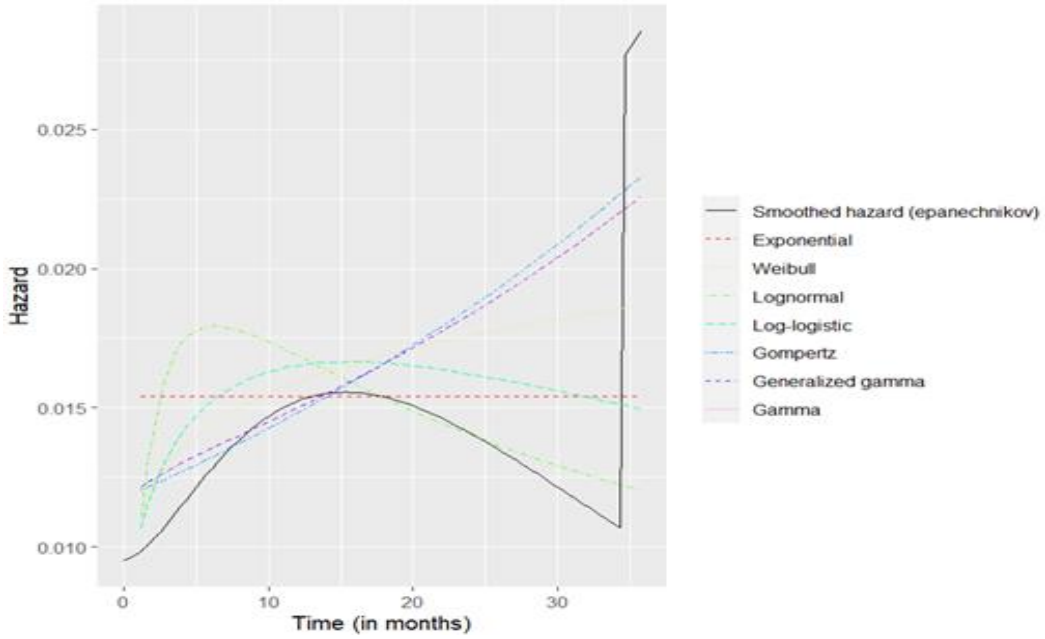

Figure 56 Smoothed hazard plots for ToT - avapritinib, IPW adjusted (censored for death)

For avapritinib, the Log-normal and Log-logistic model all generated increasing then decreasing hazard profiles both with slightly sharper short-term increase followed by a sharper decline in hazards. The Generalized Gamma, Gamma, and Gompertz model produced a steadily increasing risk of death over time. The Weibull model produced an increasing but linear hazard plot that appeared to flatten very slowly over time. Lastly, the Exponential model generated a constant risk of mortality over time.

However, it is important to note that the appropriateness of the hazard profiles produced by each parametric model for each treatment arm requires clinical expert feedback.

D.3.7 Adjustment of background mortality

Throughout the model, the mortality rate is set to be at least that of the age- and sex-adjusted general population in Denmark.

D.3.8 Adjustment for treatment switching/cross-over

Not applicable.

D.3.9 Waning effect

Linkage of ToT to OS. Refer to Appendix D.1.8.

D.3.10 Cure-point

Not applicable.

D.3.11 Validation and discussion of extrapolated curves

The ToT estimates produced by the final base case model were presented to a clinical expert. The clinical expert suggested that ToT produced by the Gompertz model are clinically plausible (52).

Appendix E. Serious adverse events

Table 73 details the serious adverse events with a frequency of >1% in the NAVIGATOR study. Table 74 details the adverse events of special interest in the NAVIGATOR study.

As shown in the table below, a total of 35 deaths were reported on treatment. Of the 35 deaths, 16 of the deaths were due to adverse events of disease progression, 6 due to general physical health deterioration, 3 death each due to sepsis and tumour haemorrhage and 1 death each due to abdominal pain, hyperbilirubinemia, respiratory failure, hepatic failure, cardiac failure, metastatic neoplasm, and schizophrenia (51). All fatal adverse events were assessed by the investigator as not related to study treatment (51).

Table 73 Serious adverse events with a frequency of >1% for avapritinib; NAVIGATOR; safety population analysis set & PDGFRA D842V 300 mg/400 mg; PDGFRA D842V all doses; January 2021 DC

Adverse events, n (%)	Avapritinib (N=250)	Avapritinib 300mg /400mg (N = 38)	Avapritinib All doses (N = 56)
Patients with ≥1 SAE	165 (66.0)	30 (78.9)	47 (83.9)
Anaemia	27 (10.8)	6 (15.8)	7 (12.5)
Disease progression	20 (8.0)	3 (7.9)	4 (7.1)
Abdominal pain	10 (4.0)	0	1 (1.8)
Sepsis	8 (3.2)	1 (2.6)	1 (1.8)
Upper gastrointestinal haemorrhage	8 (3.2)	0	2 (3.6)
General physical health deterioration	7 (2.8)	1 (2.6)	2 (3.6)
Pneumonia	7 (2.8)	2 (5.3)	2 (3.6)
Pneumonia aspiration	2 (<1)	2 (5.3)	2 (3.6)
Gastrointestinal haemorrhage	6 (2.4)	1 (2.6)	3 (5.4)
Pleural effusion	6 (2.4)	2 (5.3)	3 (5.4)
Acute kidney injury	5 (2.0)	1 (2.6)	2 (3.6)

Adverse events, n (%)	Avapritinib (N=250)	Avapritinib 300mg /400mg (N = 38)	Avapritinib All doses (N = 56)
Tumour haemorrhage	5 (2.0)	0	1 (1.8)
Vomiting	5 (2.0)	0	0
Confusional state	4 (1.6)	0	1 (1.8)
Diarrhoea	4 (1.6)	1 (2.6)	2 (3.6)
Ascites	3 (1.2)	0	0
Cerebral haemorrhage	3 (1.2)	1 (2.6)	2 (3.6)
Cognitive disorder	3 (1.2)	0	1 (1.8)
Dehydration	3 (1.2)	0	0
Encephalopathy	3 (1.2)	0	0
Gastroenteritis	3 (1.2)	2 (5.3)	3 (5.4)
Melaena	3 (1.2)	2 (5.3)	2 (3.6)
Nausea	3 (1.2)	0	0
Peritoneal haemorrhage	3 (1.2)	1 (2.6)	1 (1.8)
Small intestinal haemorrhage	3 (1.2)	1 (2.6)	1 (1.8)
Small intestinal obstruction	3 (1.2)	0	2 (3.6)
Transient ischaemic attack	3 (1.2)	1 (2.6)	1 (1.8)
Urinary tract infection	3 (1.2)	2 (5.3)	2 (3.6)
Clostridium difficile infection	2 (<1)	0	2 (3.6)
Colitis	2 (<1)	2 (5.3)	2 (3.6)
Delirium	2 (<1)	1 (2.6)	2 (3.6)
Diarrhoea	4 (1.6)	1 (2.6)	2 (3.6)

Adverse events, n (%)	Avapritinib (N=250)	Avapritinib 300mg /400mg (N = 38)	Avapritinib All doses (N = 56)
Gastric haemorrhage	2 (<1)	2 (5.3)	2 (3.6)
Myocardial infarction	2 (<1)	1 (2.6)	2 (3.6)
Upper respiratory tract infection	2 (<1)	2 (5.3)	2 (3.6)
Vertigo	2 (<1)	0	2 (3.6)
Agitation	1 (<1)	1 (2.6)	1 (1.8)
Angina pectoris	1 (<1)	1 (2.6)	1 (1.8)
Angina unstable	1 (<1)	1 (2.6)	1 (1.8)
Angioedema	1 (<1)	1 (2.6)	1 (1.8)
Benign gastric neoplasm	1 (<1)	1 (2.6)	1 (1.8)
Bronchospasm	1 (<1)	1 (2.6)	1 (1.8)
Cardiac failure	1 (<1)	1 (2.6)	1 (1.8)
Circumoral oedema	1 (<1)	1 (2.6)	1 (1.8)
Cystitis	1 (<1)	0	1 (1.8)
Dementia	2 (<1)	0	1 (1.8)
Device related infection	2 (<1)	1 (2.6)	1 (1.8)
Dyskinesia	1 (<1)	1 (2.6)	1 (1.8)
Dyspnoea	2 (<1)	1 (2.6)	1 (1.8)
Enteritis	1 (<1)	1 (2.6)	1 (1.8)
Epilepsy	1 (<1)	0	1 (1.8)
Femur fracture	1 (<1)	1 (2.6)	1 (1.8)
Forearm fracture	1 (<1)	1 (2.6)	1 (1.8)
Haemorrhage intracranial	2 (<1)	1 (2.6)	1 (1.8)
Hepatic failure	1 (<1)	0	1 (1.8)

Adverse events, n (%)	Avapritinib (N=250)	Avapritinib 300mg /400mg (N = 38)	Avapritinib All doses (N = 56)
Herpes simplex encephalitis	1 (<1)	1 (2.6)	1 (1.8)
Herpes zoster	1 (<1)	1 (2.6)	1 (1.8)
Hip fracture	1 (<1)	0	1 (1.8)
Hypoglycaemia	2 (<1)	1 (2.6)	1 (1.8)
Leiomyosarcoma	1 (<1)	1 (2.6)	1 (1.8)
Lower gastrointestinal haemorrhage	2 (<1)	1 (2.6)	1 (1.8)
Major depression	1 (<1)	0	1 (1.8)
Metastases to peritoneum	1 (<1)	1 (2.6)	1 (1.8)
Mood altered	1 (<1)	0	1 (1.8)
Nephrolithiasis	1 (<1)	1 (2.6)	1 (1.8)
Oedema peripheral	1 (<1)	0	1 (1.8)
Oesophageal squamous cell carcinoma	1 (<1)	0	1 (1.8)
Papilloedema	1 (<1)	1 (2.6)	1 (1.8)
Pericardial effusion	1 (<1)	0	1 (1.8)
Peritoneal haemorrhage	3 (1.2)	1 (2.6)	1 (1.8)
Peritonitis	1 (<1)	1 (2.6)	1 (1.8)
Peroneal nerve palsy	1 (<1)	1 (2.6)	1 (1.8)
Personality change	1 (<1)	1 (2.6)	1 (1.8)
Pneumonia escherichia	1 (<1)	1 (2.6)	1 (1.8)
Prostate cancer	1 (<1)	0	1 (1.8)
Prostatitis	1 (<1)	0	1 (1.8)
Psychotic disorder	2 (<1)	0	1 (1.8)

Adverse events, n (%)	Avapritinib (N=250)	Avapritinib 300mg /400mg (N = 38)	Avapritinib All doses (N = 56)
Pyrexia	2 (<1)	1 (2.6)	1 (1.8)
Schizophrenia	1 (<1)	1 (2.6)	1 (1.8)
Skin infection	1 (<1)	0	1 (1.8)
Syncope	1 (<1)	0	1 (1.8)
Deaths	35 (14.0)	-	-

Note: Adverse Events are coded using MedDRA 18.1. AEs refer to TEAEs which is defined as an AE that occurs during or after administration of the first dose of study drug through 30 days after the last dose of study drug, any event that is considered study drug-related regardless of the start date of the event, or any event that is present at baseline but worsens intensity or is subsequently considered study drug-related by the Investigator. All TEAEs including treatment emergent serious adverse events are included in summary statistics. If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count.

Source: NAVIGATOR CSR; Table 14.3.3.1 (51)

Table 74 Adverse events of special interest; NAVIGATOR; safety population analysis set & PDGFRA D842V 300 mg/400 mg; PDGFRA D842V all doses; January 2021 DC

Adverse events, n (%)	Avapritinib (N=250)	Avapritinib 300mg /400mg (N = 38)	Avapritinib All doses (N = 56)
Cognitive effects	116 (46.4)	NR	NR
• Memory impairment	82 (32.8)	18 (47.4)	24 (42.9)
• Cognitive disorder	29 (11.6)	5 (13.2)	8 (14.3)
• Confusional state	18 (7.2)	7 (18.4)	9 (16.1)
• Encephalopathy	5 (2.0)	0	0
Intracranial bleeding	8 (3.2)	NR	NR
• Cerebral haemorrhage	3 (1.2)	1 (2.6)	2 (3.6)
• Subdural haematoma	3 (1.2)	0	0
• Haemorrhage intracranial	2 (<1)	1 (2.6)	0

Note: Adverse Events are coded using MedDRA 18.1. If a patient has multiple occurrences of an AESI within each PT, or AESI category, the patient is presented only once in the respective patient count.

Source: NAVIGATOR CSR; Table 14.3.13.1 (51)

Appendix F. Health-related quality of life

Not applicable.

PDGFRA D842V GIST is considered significantly different from the non-mutated GIST variant included in the VOYAGER trial as well as reported in previous NICE TAs.

Since the HRQoL data is based on previous NICE TAs on the non-mutated disease and the unpublished VOYAGER trial, it might not directly capture the pertinent health states or domains of the mutated disease, hence potentially misrepresenting health states and impacts of the PDGFRA D842V mutation.

Appendix G. Probabilistic sensitivity analyses

Table 75 shows the distributional assumptions of model parameters.

Table 75 Overview of parameters in the Probabilistic sensitivity analyses (PSA)

Input parameter	Point estimate	Lower bound	Upper bound	SE	Probability distribution
Population characteristics					
Initial age	61.70	49.61	73	6.17	Gamma
Proportion of males	65.8	52.5	77.9	6.6	Beta
Clinical					
Avapritinib OS, lognormal - _cons	10.1905				Normal
Avapritinib OS, lognormal – sigma	3.2960				Normal
ECM OS, Weibull - _cons	-1.8154				Normal
ECM OS, Weibull - p	0.6399				Normal
Avapritinib PFS, Weibull - _cons	-5.4243				Normal
Avapritinib PFS, Weibull – p	1.3536				Normal
ECM PFS 1L, Weibull - _cons	-1.2524				Normal
ECM PFS 1L, Weibull - p	0.8540				Normal
ECM PFS 2L, exponential - cons	-1.7689				Normal
ECM PFS 3L, exponential - cons	-2.4843				Normal

Avapritinib ToT, Gompertz - _cons	-4.3084				Normal
Avapritinib OS, Gompertz – gamma	0.0077				Normal
HSUV					
PF1L	0.935	0.683	1.00	0.094	Beta
PF2L	0.781	0.614	0.911	0.078	Beta
PF3L	0.782	0.614	0.911	0.078	Beta
PD	0.727	0.576	0.855	0.073	Beta
Adverse events					
Duration of AE effect (days)	7.0	5.6	8.4	0.7	Gamma
Anaemia, incidence - AVA	0.0151	0.0121	0.0181	0.0015	Gamma
Decreased appetite, incidence – AVA	0.0019	0.0015	0.0023	0.0002	Gamma
Diarrhoea, incidence – AVA	0.0031	0.0025	0.0038	0.0003	Gamma
Dyspnoea, incidence – AVA	0.0019	0.0015	0.0023	0.0002	Gamma
Hypertension, incidence – AVA	0.0019	0.0015	0.0023	0.0002	Gamma
Hypokalaemia, incidence – AVA	0.0025	0.0020	0.0030	0.0003	Gamma
Neutropenia, incidence AVA	0.0031	0.0025	0.0038	0.0003	Gamma
Neutrophil count decreased, incidence - AVA	0.0038	0.0030	0.0045	0.0004	Gamma

Pleural effusion, incidence – AVA	0.0025	0.0020	0.0030	0.0003	Gamma
Pleural effusion, incidence – IMA	0.0025	0.0020	0.0030	0.0003	Gamma
Pneumonia, incidence – AVA	0.0019	0.0015	0.0023	0.0002	Gamma
Pneumonia, incidence – IMA	0.0019	0.0015	0.0023	0.0002	Gamma
Costs					
Disease management					
PF, one-off	11,964.30	9,619.30	14,309,30	1,196.43	Gamma
PF 1L/2L/3L, per cycle	4,441.45	3,570.93	5,311.97	444.14	Gamma
PD, one-off	17,881.45	14,376.69	21,386.21	1,788.15	Gamma
PD, per cycle	4,795.40	3,855.50	5,735.30	479.54	Gamma
Patient time / transportation costs					
PF, per cycle	227.78	223.33	332.22	27.78	Gamma
PD, per cycle	401.12	332.50	479.74	40.11	Gamma
Adverse events costs					
Abdominal pain	7,530	6054.12	9005.88	753	Gamma
Abnormal liver function results	4,728	3801.31	5654.68	472.8	Gamma
Anaemia	40,106	32245.22	47966.77	4010.6	Gamma
Ascites	27,085	21776.34	32393.66	2708.5	Gamma
Asthenia	4,728	3801.31	5654.68	472.8	Gamma
Blood bilirubin increased	Not taken into account				

Cognitive effects	26,400	21225.60	31574.40	2640	Gamma
Decreased appetite	20,850	16763.40	24936.60	2085	Gamma
Diarrhoea	7,530	6054.12	9005.88	753	Gamma
Dermatitis / Rash	19,941	16032.56	23849.43	1994.10	Gamma
Dyspnoea	21,632	17392.12	25871.87	2163.2	Gamma
Fatigue	4,728	3801.31	5654.68	472.8	Gamma
Edema	4,728	3801.31	5654.68	472.8	Gamma
Hemorrhage	2,089	1679.55	2498.44	208.9	Gamma
Hypertension	17,304	13912.41	20695.58	1730.4	Gamma
Hypokalaemia	26,368	21199.87	31536.12	2636.8	Gamma
Hyponatraemia	26,368	21199.87	31536.12	2636.8	Gamma
Hypophosphataemia	39,158	31483.03	46832.96	3915.8	Gamma
Leukopenia	26,179	21047.91	31310.08	2617.9	Gamma
Lymphopenia	26,179	21047.91	31310.08	2617.9	Gamma
Nausea	7,530	6054.12	9005.88	753	Gamma
Neutropenia	38,209	30720.03	45697.96	3820.9	Gamma
Neutrophil count decreased	Not taken into account				
Pleural effusion	36,350	29225.40	43474.60	3635	Gamma
Hypocalcaemia	39,158.00	31,483.032	46,832.968	3915.80	Gamma
Clostridium difficile infection	7,530.00	6,054.120	9,005.880	753.00	Gamma
Disease progression	37,945.00	30,507.780	45,382.220	3794.50	Gamma

Table 76 shows the economic results from the PSA.

Table 76 Results of the PSA

	Avapritinib	ECM	Incremental
Costs (DKK)			
Base case	3,420,420	130,592	3,289,828
PSA mean	3,271,368	132,252	3,139,116
PSA 95% CI lower	2,475,026	51,540	2,374,979
PSA 95% CI upper	4,221,079	266,068	4,026,470
QALY			
Base case	5.92	1.38	4.54
PSA mean	5.64	1.39	4.24
PSA 95% CI lower	3.37	0.45	2.49
PSA 95% CI upper	8.24	3.02	6.16
ICER (DKK/QALY)			
Base case: 724,751			
PSA mean: 739,545			
PSA 95% CI lower: 533,772			
PSA 95% CI upper: 1,138,712			

Appendix H. Literature searches for the clinical assessment
Literature searches for the clinical assessment

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

A global SLR was conducted which aimed to address the following research question:

- To evaluate and summarise evidence pertaining to the efficacy, safety and tolerability of treatment options used in patients unresectable and/or metastatic GIST harbouring the PDGFRA D842V mutation.

In order to adapt the global SLR into the context of this submission dossier for the DMC, it will be necessary to narrow down the inclusion and exclusion criteria of the original PICO-T described in Table 84, specifically the interventions of interest, as the interventions searched in the global SLR is much wider in scope compared to treatments offered in Denmark. As mentioned in section 3.3, imatinib, sunitinib and regorafenib are considered the most appropriate comparators in Denmark for this patient population. All other criteria's are to remain unchanged as they still remain relevant for this application.

The inclusion and exclusion criteria in Table 84 has been adapted to show a separate Danish specific inclusion and exclusion criteria for this submission, from which, the study selection for this assessment will be based on. The global inclusion and exclusion criteria can be seen in Table 84 for full transparency on how the search strings were developed and how the adaption was done.

As detailed in Table 77 and Table 78, the clinical SLR search was conducted on 29 June 2023.

The searches were performed in the following indexed databases via OVID:

- Embase® (via Ovid.com)
- MEDLINE® and Epub Ahead of Print, In-Process, In-Data-review & Other Non-Indexed Citations, Daily and Versions (via Ovid.com)
- Cochrane Central Register of Controlled Trials (CCTR) (via Ovid.com)
- Cochrane Database of Systematic Reviews (CDSR) (via Ovid.com)
- Database of Abstracts of Review of Effects (DARE) (via Ovid.com)
- Health Technology Assessment (HTA) Database (via Ovid.com)
- Centre for Review and Dissemination (via Ovid.com)

Electronic searching in the literature databases was not limited according to timeframe because clinical outcomes is generally advised not to limit electronic searching by time frame. The searches were not limited to English language.

Bibliographies of systematic reviews were screened to ensure that initial searches captured all the relevant utility studies.

In addition to the databases, proceedings of 3 conferences were searched for the last 2 years (2021–2023) to identify any studies of interest. These included:

- American Society of Clinical Oncology (ASCO) Annual meeting
- American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium
- European Society for Medical Oncology (ESMO) Congress

Table 77 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Medline and Medline In-Process	Ovid	1946 – 28 June 2023	29 June 2023
Embase	Ovid	1974 – 28 June 2023	29 June 2023
CCTR	Ovid	From April 2023	29 June 2023
CDSR	Ovid	2005 – 27 June 2023	29 June 2023
DARE	Ovid	1st Quarter 2016	22 June 2023
HTA	Ovid	4th Quarter 2016	22 June 2023
CRD	Ovid	Unlimited	22 June 2023

Abbreviations: CCTR = Cochrane Central Register of Controlled Trials; CDSR = Cochrane Database of Systematic Reviews; CRD = Centre for Review and Dissemination; DARE = Database of Abstracts of Reviews of Effects; HTA = Health Technology Assessment

Table 78 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
ASCO General meeting	https://meetings.asco.org/abstracts-presentations/search?query=*&q=*&sortBy=AbstractBrowse&filters=%7B%22presentationType%22:%5B%7B%22key%22:%22Abstract%20Presentation%22%7D,%7B%22key%22:%22Poster%22%7D,%7B%22key%22:%22Abs	Electronic search	gastrointestinal gastro-intestinal gastro intestinal gastrointestinal stromal stromal gist	23 June 2023

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
	tract%22%7D%5D,%22meetingTypeName%22:%5B%7B%22key%22:%22ASCO%20Annual%20Meeting%22%7D%5D,%22meetingYear%22:%5B%7B%22key%22:%222021%22%7D%5D%7D&size=50			
ASCO Gastrointestinal Cancers Symposium	https://meetings.asco.org/abstracts-presentations/search?query=*&q=*&sortBy=AbstractBrowse&filters=%7B%22presentationType%22:%5B%7B%22key%22:%22Abstract%20Presentation%22%7D,%7B%22key%22:%22Poster%22%7D,%7B%22key%22:%22Abstract%22%7D%5D,%22meetingYear%22:%5B%7B%22key%22:%222021%22%7D%5D,%22meetingTypeName%22:%5B%7B%22key%22:%22Gastrointestinal%20Cancers%20Symposium%22%7D%5D%7D&size=50	Electronic search	gastrointestinal gastro-intestinal gastro intestinal gastrointestinal stromal stromal gist	23 June 2023
ESMO	https://oncologypro.esmo.org/meeting-resources/esmo-congress	Electronic search	gastrointestinal gastro-intestinal gastro intestinal gastrointestinal stromal stromal gist	23 June 2023

Abbreviations: ASCO = American Society of Clinical Oncology; ESMO = European Society of Medical Oncology

H.1.1 Search strategies

The search strategies were based on the PICOS-T developed for this clinical SLR (Table 84). Relevant MeSH and Emtree terms were used in the relevant databases as well as free text terms.

Table 79 to Table 83 present the search hits in Medline, Embase, Cochrane databases and EBM.

Table 79 Search strategy for Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations

No.	Query	Results
#1	exp Gastrointestinal Stromal Tumors/	7694
#2	("gastrointestinal stromal tumour*" or "gastrointestinal stromal tumor*" or "gastro-intestinal stromal tumour*" or "gastro-intestinal stromal tumor*" or gist).tw.	12968
#3	1 or 2	13904
#4	(nilotinib or tasigna or "amn-107" or "amn 107" or amn107).tw.	2495
#5	(regorafenib or stivarga or resihance or "bay 73 4506" or "bay 73-4506" or "bay 734506" or "bay73 4506" or "bay73-4506" or bay734506).tw.	1775
#6	exp Imatinib Mesylate/	11503
#7	(imatinib or gleevac or gleevec or glivec or glivic or ruvise or "cgp 57148" or "cgp-57148*" or cgp57148* or "signal transduction inhibitor 571" or "st 1571" or st1571 or "sti 571" or "sti-571" or sti571 or "st-1571" or "220127-57-1" or "8a1o1m485b" or "bkj8m8g5hi" or "aer 901" or "aer901" or "av 101" or "av101" or egitinib or glipox or imagerolan or imakrebin or imanivec or imaniver or imarem or imatek or imatenil or imatilek or impentri or itivas or latib or leutipol or leuzek or meaxin or nibix or plivatinib or "qti 571" or "qti571" or vianib or "vr 325" or "vr325" or "yd 312" or "yd312").tw.	16188
#8	exp Sorafenib/	6275
#9	(sorafenib or nexavar or "bay 43 9006" or "bay 43-9006" or "bay 439006" or "bay43 9006" or "bay43-9006" or bay439006 or "bay 54 9085" or "bay 549085" or "bay54 9085" or bay549085 or fenesa or "hynap-sora" or reniloxa or revamox or rexanib or sorafeb or soratina or weldinin).tw.	10882
#10	(pazopanib or armala or votrient or "gw 786034*" or "gw-786034*" or "gw 786034x" or gw786034 or gw786034b or gw786034x or "sb 710468" or "sb 710468a" or sb710468 or sb710468a).tw.	2138
#11	(olaratumab or lartruvo or "imc 3g3" or imc3g3 or "ly 3012207" or ly3012207 or "ly-3012207").tw.	112
#12	(dovitinib or "chir 258" or chir258 or "chir-258" or "tki 258" or tki258 or "tki-258").tw.	207
#13	exp Dasatinib/	2598
#14	(dasatinib or sprycel or uxil or "bms 354825*" or "bms-354825*" or "bms 354825 03" or "bms 354825-03" or "bms 35482503" or bms354825 or "bms354825 03" or "bms354825-03" or bms35482503).tw.	4079

No.	Query	Results
#15	(pexidartinib or turalio or "cml 261" or cml261 or "fp 113" or fp113 or "plexxikon 3397" or plexxikon3397 or "plx 3397" or plx3397 or "plx-3397").tw.	256
#16	(vismodegib or erivedge or "gdc 0449" or "gdc-0449" or gdc0449 or "Hhantag 691" or Hhantag691 or "rg 3616" or rg3616).tw.	899
#17	exp Panobinostat/	628
#18	(panobinostat or farydak or "lbh 589" or "lbh 589a" or "lbh 589b" or lbh589 or lbh589a or lbh589b or "mtx 110" or matx110 or "nvp lbh 589" or "nvp lbh589").tw.	1036
#19	(buparlisib or "bkm 120*" or "bkm-120*" or "bkm 120 aaa" or "bkm 120 nx" or "bkm 120aaa" or "bkm 120nx" or bkm120 or "bkm120 aaa" or "bkm120 nx" or bkm120aaa or bkm120nx or "nvp bkm 120" or "nvp bkm120").tw.	382
#20	(alpelisib or pigray or vijoice or "byl 719" or "byl-719" or byl719 or "nvp byl 719" or "nvp byl719").tw.	418
#21	(luminespib or "auy 922" or "auy-922" or auy922 or "nvp auy 922" or "nvp auy 922 agb" or "nvp auy 922 nx" or "nvp auy922" or "nvp auy922 agb" or "nvp auy922 nx" or "ver 52296" or ver52296).tw.	252
#22	(onalespib or "at 13387*" or "at-13387*" or "at 13387a" or "at 13387au" or "at 13387x" or at13387 or at13387a or at13387au or at13387x).tw.	62
#23	(ganetespib or "sta 9090" or sta9090 or "sta-9090").tw.	168
#24	exp Everolimus/	5644
#25	(everolimus or affinitor or afinitor or certican or votubia or zortress or "nvp rad 001" or "nvp rad001" or "rad 001*" or "rad-001*" or "rad 001a" or rad001 or rad001a or "sdz rad" or rad666).tw.	7971
#26	exp Nivolumab/	5136
#27	(nivolumab or opdivo or "bms 936558" or "bms-936558" or bms936558 or "cmab 819" or "cmab-819" or cmab819 or "mdx 1106" or mdx1106 or "ono 4538" or ono4538).tw.	8134
#28	exp Ipilimumab/	2919
#29	(ipilimumab or strentarga or yervoy or "bms-734016" or "bms 734016" or "cs 1002" or cs1002 or "ibi 310" or ibi310 or bms734016 or "mdx 010" or "mdx-010" or "mdx 101" or mdx010 or mdx101).tw.	4537
#30	(masitinib or alsitek or kinaction or masatinib or masican or masipro or masivet or masiviera or "ab 1010" or "ab-1010" or ab1010).tw.	179

No.	Query	Results
#31	exp Temozolomide/	5944
#32	(temozolomide or temcad or temodal or temodar or temodex or temodol or temomedac or temoxol or methazolastone or kimozo or "ccrg 81045" or "ccrg-81045" or ccrg81045 or "m and b 39831" or "m b 39831" or "mb 39831" or mb39831 or "mk 7365" or mk7365 or "nsc 362856" or "nsc-362856" or nsc362856 or "orp 005" or orp005 or "rp 46161" or rp46161 or "sch 052365" or "sch 52365" or sch052365 or "si 053" or si053).tw.	9514
#33	(binimetinib or balimek or mektovi or "arry 162" or "arry-162" or "arry 438162" or arry162 or arry438162 or "mek 162" or mek162 or "mek-162" or "ono 7703" or ono7703 or "pf 06811462" or "pf 6811462" or pf06811462 or pf6811462).tw.	314
#34	(motesanib or "amg 706" or "amg-706" or amg706).tw.	111
#35	(infigratinib or truseltig or "bbp 831" or bbp831 or "bgj 398" or bgj398 or "nvp bgj 398" or "nvp bgj398").tw.	201
#36	exp Sunitinib/	4153
#37	(sunitinib or sutent or "pha 2909040ad" or pha2909040ad or "su 010398" or "su 011248" or "su 10398" or "su 11248" or su010398 or su011248 or su10398 or su11248 or "suo 11248" or suo11248 or "gb 102" or gb102).tw.	6799
#38	(avapritinib or "blu 285" or "blu-285" or blu285 or "70c366" or ayvakit or ayvakyt* or "blu 112317" or "blu112317" or "c 366" or "c366" or "cs 3007" or "cs3007" or "x 720776" or "x720776").tw.	182
#39	(ripretinib or ginlock or dcc2618 or "dcc 2618").tw.	105
#40	(cediranib or recentin or zemfirza or "azd 2171" or "azd-2171" or azd2171).tw.	400
#41	(cabozantinib or cometriq or cabometyx or "bms 907351" or "bms-907351" or bms907351 or "xl 184" or xl184).tw.	1465
#42	(ponatinib or iclusig or "ap 24534" or "ap-24534" or ap24534).tw.	966
#43	(linsitinib or "osi 906" or "osi 906aa" or "osi-906" or osi906 or osi906aa).tw.	166
#44	(vandetinib or zactima or caprelsa or zictifa or "azd 6474" or "azd-6474" or azd6474 or "zd 6474" or zd6474 or "zd-6474" or "sar 390530" or sar390530).tw.	235
#45	(vatalanib or nublox or "cgp 79787" or "cgp 79787d" or "cgp-79787" or cgp79787 or cgp79787d or "ptk 787" or ptk787 or "ptk-787" or "zk 222584" or zk222584).tw.	338

No.	Query	Results
#46	(crenolanib or "aro 002" or "aro 002 26" or "aro 002-26" or "aro-002" or aro002 or "aro002 26" or "aro002-26" or "cp 868596" or "cp 868596 26" or "cp 868596-26" or cp868596 or "cp868596 26" or "cp868596-26").tw.	98
#47	(amcasertib or "bbi 503" or bbi503 or "bbi-503").tw.	0
#48	(palbociclib or ibrance or "pd 0332991" or "pd 0332991 0054" or "pd 0332991-0054" or "pd 332991" or pd0332991 or "pd0332991 0054" or "pd0332991-0054" or pd332991 or "pf 00080665 73" or "pf 00080665-73" or "pf00080665 73" or "pf00080665-73").tw.	1649
#49	(pembrolizumab or keytruda or lambrolizumab or "mk 3475" or mk3475 or "sch 900475" or sch900475).tw.	7496
#50	exp Albumin-Bound Paclitaxel/ or exp Paclitaxel/	30778
#51	(paclitaxel or "albumin bound paclitaxel" or "albumin-bound paclitaxel" or "nab paclitaxel" or "nanoparticle albumin bound paclitaxel" or abraxane or abraxus or anzatax or apealea or asotax or biotax or bristaxol or britaxol or coroxane or "endotag-1" or formoxol or genexol or "genexol pm" or hunxol or ifaxol or infinnium or intaxel or liporaxel or medixel or mitotax or nanopac or nanotax or oncogel or onxol or pacitaxel or "paclitaxel nab" or pacxel or padexol or parexel or paxceed or paxene or paxus or pazenir or praxel or taxocris or taxol or taycovit or yewtaxan or "abi 007" or abi007 or "bms 181339" or bms181339 or "bmy 45622" or bmy45622 or "dhp 107" or dhp107 or "dts 301" or dts301 or "fid 007" or fid007 or "mbt 0206" or mbt0206 or "nk 105" or nk105 or "nsc 125973" or "nsc 673089" or nsc125973 or nsc673089 or "oas pac 100" or oaspac100 or "sb 05" or sb05).tw.	41100
#52	(dabrafenib or tafinlar or "drb 436" or drb436 or "gsk 2118436" or "gsk 2118436a" or "gsk 2118436b" or gsk2118436 or gsk2118436a or gsk2118436b).tw.	1487
#53	(trametinib or mekinist or "gsk 1120212" or "gsk 1120212b" or gsk1120212 or gsk1120212b or "jtp 74057" or jtp74057 or "snr 1611" or snr1611 or "tmt 212" or tmt212).tw.	1869
#54	(amuvatinib or bez235 or "bez 235" or "bez-235" or "hpk 56" or hpk56 or "mp 470" or mp470).tw.	658
#55	(retaspimycin or tanespimycin or "ipi 504" or "ipi-504" or ipi504).tw.	151
#56	(xl820 or "xl 820" or "xl-820").tw.	2
#57	(hqp1351 or "hqp-1351" or "hqp 1351").tw.	11
#58	(tidutamab or xmab18087 or "xmab 18087").tw.	0

No.	Query	Results
#59	("dp-3636" or "dp 3636" or dp3636 or "dp-4444" or "dp 4444" or dp4444 or "dp 4851" or "dp-4851" or dp4854 or "biib 021" or biib021 or lor628 or "lor 628" or "lor-628" or "dp 2976" or dp2976).tw.	45
#60	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59	126927
#61	(Randomized Controlled Trials as Topic/ or randomized controlled trial/ or Random Allocation/ or Double Blind Method/ or Single Blind Method/ or clinical trial/ or clinical trial, phase i.pt. or clinical trial, phase ii.pt. or clinical trial, phase iii.pt. or clinical trial, phase iv.pt. or randomized controlled trial.pt. or multicenter study.pt. or clinical trial.pt. or exp Clinical Trials as topic/ or (clinical adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind*3 or mask*3)).tw. or PLACEBOS/ or placebo*.tw. or randomly allocated.tw. or (allocated adj2 random*).tw. or "randomi?ed controlled trial*".tw. or rct.tw. or (random* adj2 allocat*).tw.) not (case report.tw. or letter/ or historical article/)	1928569
#62	Epidemiologic studies/ or exp case control studies/ or exp cohort studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy*.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective.tw. or Cross sectional.tw. or Cross-sectional studies/ or (Case control adj (study or studies)).tw. or (epidemiologic* adj (study or studies)).tw. or (cross sectional adj (study or studies)).tw. or (exp Prospective Studies/ not exp Randomized Controlled Trial/)	3849470
#63	(single-arm or "single arm" or non-comparative or "non comparative" or nonRCT or non-RCT or "non RCT" or "no random*" or "not random*" or "non random*" or "non-random*").tw. or exp Comparative Study/ or cohort.mp. or compared.mp. or groups.mp. or multivariate.mp.	7951532
#64	61 or 62 or 63	10427418
#65	3 and 60 and 64	1781
#66	("Case Reports" or Comment or Editorial or Letter).pt.	4284226
#67	exp Animals/ not (exp Animals/ and exp Humans/)	5133797
#68	66 or 67	9307346
#69	65 not 68	1637

Table 80 Search strategy for Embase

No.	Query	Results
#1	exp gastrointestinal stromal tumor/	21133
#2	("gastrointestinal stromal tumour*" OR "gastrointestinal stromal tumor*" OR "gastro-intestinal stromal tumour*" OR "gastro-intestinal stromal tumor*" OR gist).tw.	20207
#3	1 or 2	26320
#4	exp nilotinib/	11214
#5	(nilotinib or tasigna or "amn-107" or "amn 107" or amn107).tw.	6997
#6	exp regorafenib/	6761
#7	(regorafenib or stivarga or resihance or "bay 73 4506" or "bay 73-4506" or "bay 734506" or "bay73 4506" or "bay73-4506" or bay734506).tw.	3929
#8	exp imatinib/	48786
#9	(imatinib or gleevac or gleevec or glivec or glivic or ruvise or "cgp 57148" or "cgp-57148*" or cgp57148* or "signal transduction inhibitor 571" or "st 1571" or st1571 or "sti 571" or "sti-571" or sti571 or "st-1571" or "220127-57-1" or "8a1o1m485b" or "bkj8m8g5hi" or "aer 901" or "aer901" or "av 101" or "av101" or egitinib or glipox or imagerolan or imakrebin or imanivec or imaniver or imarem or imatek or imatenil or imatilek or impentri or itivas or latib or leutipol or leuzek or meaxin or nibix or plivatinib or "qti 571" or "qti571" or vianib or "vr 325" or "vr325" or "yd 312" or "yd312").tw.	33899
#10	exp sorafenib/	37776
#11	(sorafenib or nexavar or "bay 43 9006" or "bay 43-9006" or "bay 439006" or "bay43 9006" or "bay43-9006" or bay439006 or "bay 54 9085" or "bay 549085" or "bay54 9085" or bay549085 or fenesa or "hynap-sora" or reniloxa or revamox or rexanib or sorafeb or soratina or weldinin).tw.	22934
#12	exp pazopanib/	10710
#13	(pazopanib or armala or votrient or "gw 786034*" or "gw-786034*" or "gw 786034x" or gw786034 or gw786034b or gw786034x or "sb 710468" or "sb 710468a" or sb710468 or sb710468a).tw.	5048
#14	exp olaratumab/	546
#15	(olaratumab or lartruvo or "imc 3g3" or imc3g3 or "ly 3012207" or ly3012207 or "ly-3012207").tw.	288
#16	exp dovitinib/	1169

No.	Query	Results
#17	(dovitinib or "chir 258" or chir258 or "chir-258" or "tki 258" or tki258 or "tki-258").tw.	705
#18	exp dasatinib/	17669
#19	(dasatinib or sprycel or uxil or "bms 354825*" or "bms-354825*" or "bms 354825 03" or "bms 354825-03" or "bms 35482503" or bms354825 or "bms354825 03" or "bms354825-03" or bms35482503).tw.	10280
#20	exp pexidartinib/	735
#21	(pexidartinib or turalio or "cml 261" or cml261 or "fp 113" or fp113 or "plexxikon 3397" or plexxikon3397 or "plx 3397" or plx3397 or "plx-3397").tw.	657
#22	exp vismodegib/	2769
#23	(vismodegib or erivedge or "gdc 0449" or "gdc-0449" or gdc0449 or "Hhantag 691" or Hhantag691 or "rg 3616" or rg3616).tw.	2045
#24	exp panobinostat/	5124
#25	(panobinostat or farydak or "lbh 589" or "lbh 589a" or "lbh 589b" or lbh589 or lbh589a or lbh589b or "mtx 110" or matx110 or "nvp lbh 589" or "nvp lbh589").tw.	3190
#26	exp buparlisib/	2099
#27	(buparlisib or "bkm 120*" or "bkm-120*" or "bkm 120 aaa" or "bkm 120 nx" or "bkm 120aaa" or "bkm 120nx" or bkm120 or "bkm120 aaa" or "bkm120 nx" or bkm120aaa or bkm120nx or "nvp bkm 120" or "nvp bkm120").tw.	1656
#28	exp alpelisib/	1903
#29	(alpelisib or pigray or vijoice or "byl 719" or "byl-719" or byl719 or "nvp byl 719" or "nvp byl719").tw.	1447
#30	exp luminespib/	692
#31	(luminespib or "auy 922" or "auy-922" or auy922 or "nvp auy 922" or "nvp auy 922 agb" or "nvp auy 922 nx" or "nvp auy922" or "nvp auy922 agb" or "nvp auy922 nx" or "ver 52296" or ver52296).tw.	836
#32	exp onalespib/	229
#33	(onalespib or "at 13387*" or "at-13387*" or "at 13387a" or "at 13387au" or "at 13387x" or at13387 or at13387a or at13387au or at13387x).tw.	278
#34	exp ganetespib/	854

No.	Query	Results
#35	(ganetespib or "sta 9090" or sta9090 or "sta-9090").tw.	585
#36	exp everolimus/	36108
#37	(everolimus or affinitor or afinitor or certican or votubia or zortress or "nvp rad 001" or "nvp rad001" or "rad 001*" or "rad-001*" or "rad 001a" or rad001 or rad001a or "sdz rad" or rad666).tw.	20656
#38	exp nivolumab/	37075
#39	(nivolumab or opdivo or "bms 936558" or "bms-936558" or bms936558 or "cmab 819" or "cmab-819" or cmab819 or "mdx 1106" or mdx1106 or "ono 4538" or ono4538).tw.	20749
#40	exp ipilimumab/	24219
#41	(ipilimumab or strentarga or yervoy or "bms-734016" or "bms 734016" or "cs 1002" or cs1002 or "ibi 310" or ibi310 or bms734016 or "mdx 010" or "mdx-010" or "mdx 101" or mdx010 or mdx101).tw.	11645
#42	exp masitinib/	763
#43	(masitinib or alsitek or kinaction or masatinib or masican or masipro or masivet or masiviera or "ab 1010" or "ab-1010" or ab1010).tw.	367
#44	exp temozolomide/	32440
#45	(temozolomide or temcad or temodal or temodar or temodex or temodol or temomedac or temoxol or methazolastone or kimozo or "ccrg 81045" or "ccrg-81045" or ccrg81045 or "m and b 39831" or "m b 39831" or "mb 39831" or mb39831 or "mk 7365" or mk7365 or "nsc 362856" or "nsc-362856" or nsc362856 or "orp 005" or orp005 or "rp 46161" or rp46161 or "sch 052365" or "sch 52365" or sch052365 or "si 053" or si053).tw.	18525
#46	exp binimetinib/	1903
#47	(binimetinib or balimek or mektovi or "arry 162" or "arry-162" or "arry 438162" or arry162 or arry438162 or "mek 162" or mek162 or "mek-162" or "ono 7703" or ono7703 or "pf 06811462" or "pf 6811462" or pf06811462 or pf6811462).tw.	1040
#48	exp motesanib/	844
#49	(motesanib or "amg 706" or "amg-706" or amg706).tw.	603
#50	exp infigratinib/	872
#51	(infigratinib or truseltig or "bbp 831" or bbp831 or "bgj 398" or bgj398 or "nvp bgj 398" or "nvp bgj398").tw.	738

No.	Query	Results
#52	exp sunitinib/	27563
#53	(sunitinib or sutent or "pha 2909040ad" or pha2909040ad or "su 010398" or "su 011248" or "su 10398" or "su 11248" or su010398 or su011248 or su10398 or su11248 or "suo 11248" or suo11248 or "gb 102" or gb102).tw.	15645
#54	exp avapritinib/	463
#55	(avapritinib or "blu 285" or "blu-285" or blu285 or "70c366" or ayvakit or ayvakyt* or "blu 112317" or "blu112317" or "c 366" or "c366" or "cs 3007" or "cs3007" or "x 720776" or "x720776").tw.	397
#56	exp ripretinib/	293
#57	(ripretinib or ginlock or dcc2618 or "dcc 2618").tw.	215
#58	exp cediranib/	3047
#59	(cediranib or recentin or zemfirza or "azd 2171" or "azd-2171" or azd2171).tw.	1649
#60	exp cabozantinib/	6801
#61	(cabozantinib or cometriq or cabometyx or "bms 907351" or "bms-907351" or bms907351 or "xl 184" or xl184).tw.	3781
#62	exp ponatinib/	4342
#63	(ponatinib or iclusig or "ap 24534" or "ap-24534" or ap24534).tw.	2609
#64	exp linsitinib/	623
#65	(linsitinib or "osi 906" or "osi 906aa" or "osi-906" or osi906 or osi906aa).tw.	560
#66	exp vandetanib/	5426
#67	(vandetinib or zactima or caprelsa or zictifa or "azd 6474" or "azd-6474" or azd6474 or "zd 6474" or zd6474 or "zd-6474" or "sar 390530" or sar390530).tw.	2006
#68	exp vatalanib/	2635
#69	(vatalanib or nublox or "cgp 79787" or "cgp 79787d" or "cgp-79787" or cgp79787 or cgp79787d or "ptk 787" or ptk787 or "ptk-787" or "zk 222584" or zk222584).tw.	1854
#70	exp crenolanib/	702

No.	Query	Results
#71	(crenolanib or "aro 002" or "aro 002 26" or "aro 002-26" or "aro-002" or aro002 or "aro002 26" or "aro002-26" or "cp 868596" or "cp 868596 26" or "cp 868596-26" or cp868596 or "cp868596 26" or "cp868596-26").tw.	317
#72	exp amcasertib/	29
#73	(amcasertib or "bbi 503" or bbi503 or "bbi-503").tw.	24
#74	exp palbociclib/	6541
#75	(palbociclib or ibrance or "pd 0332991" or "pd 0332991 0054" or "pd 0332991-0054" or "pd 332991" or pd0332991 or "pd0332991 0054" or "pd0332991-0054" or pd332991 or "pf 00080665 73" or "pf 00080665-73" or "pf00080665 73" or "pf00080665-73").tw.	4526
#76	exp pembrolizumab/	35948
#77	(pembrolizumab or keytruda or lambrolizumab or "mk 3475" or mk3475 or "sch 900475" or sch900475).tw.	19736
#78	exp paclitaxel/	133789
#79	(paclitaxel or "albumin bound paclitaxel" or "albumin-bound paclitaxel" or "nab paclitaxel" or "nanoparticle albumin bound paclitaxel" or abraxane or abraxus or anzatax or apealea or asotax or biotax or bristaxol or britaxol or coroxane or "endotag-1" or formoxol or genexol or "genexol pm" or hunxol or ifaxol or infinnium or intaxel or liporaxel or medixel or mitotax or nanopac or nanotax or oncogel or onxol or pacitaxel or "paclitaxel nab" or pacxel or padexol or parexel or paxceed or paxene or paxus or pazenir or praxel or taxocris or taxol or taycovit or yewtaxan or "abi 007" or abi007 or "bms 181339" or bms181339 or "bmy 45622" or bmy45622 or "dhp 107" or dhp107 or "dts 301" or dts301 or "fid 007" or fid007 or "mbt 0206" or mbt0206 or "nk 105" or nk105 or "nsc 125973" or "nsc 673089" or nsc125973 or nsc673089 or "oas pac 100" or oaspac100 or "sb 05" or sb05).tw.	72027
#80	exp dabrafenib/	6967
#81	(dabrafenib or tafinlar or "drb 436" or drb436 or "gsk 2118436" or "gsk 2118436a" or "gsk 2118436b" or gsk2118436 or gsk2118436a or gsk2118436b).tw.	3547
#82	exp trametinib/	8994
#83	(trametinib or mekinist or "gsk 1120212" or "gsk 1120212b" or gsk1120212 or gsk1120212b or "jtp 74057" or jtp74057 or "snr 1611" or snr1611 or "tmt 212" or tmt212).tw.	4736
#84	exp amuvatinib/	109

No.	Query	Results
#85	(amuvatinib or bez235 or "bez 235" or "bez-235" or "hpk 56" or hpk56 or "mp 470" or mp470).tw.	2501
#86	exp retaspimycin/	292
#87	(retaspimycin or tanespimycin or "ipi 504" or "ipi-504" or ipi504).tw.	527
#88	(xl820 or "xl 820" or "xl-820").tw.	26
#89	(hqp1351 or "hqp-1351" or "hqp 1351").tw.	48
#90	exp tidutamab/	10
#91	(tidutamab or xmab18087 or "xmab 18087").tw.	11
#92	("dp-3636" or "dp 3636" or dp3636 or "dp-4444" or "dp 4444" or dp4444 or "dp 4851" or "dp-4851" or dp4854 or "biib 021" or biib021 or lor628 or "lor 628" or "lor-628" or "dp 2976" or dp2976).tw.	164
#93	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92	376548
#94	(exp clinical trial/ or exp control group/ or exp randomized controlled trial/ or exp randomization/ or single blind procedure/ or double blind procedure/ or crossover procedure/ or exp placebo/ or exp controlled clinical trial/ or exp placebo effect/ or Random Allocation/ or Double Blind Method/ or Single Blind Method/ or PLACEBOS/ or multicenter study/ or Phase 3 clinical trial/ or Phase 4 clinical trial/ or Prospective Study/ or "randomi?ed controlled trial*".tw. or rct.tw. or (random* adj2 allocat*).tw. or "single blind*".tw. or "double blind*".tw. or ((treble or triple) adj blind*).tw. or placebo*.tw. or (clinical adj trial*).tw.) not (case study/ or "case report".ab,ti. or abstract report/ or letter/)	3375713
#95	Clinical study/ or Case control study/ or Family study/ or Longitudinal study/ or Retrospective study/ or (Prospective study/ not Randomized controlled trials/) or Cohort analysis/ or (Cohort adj (study or studies)).mp. or (Case control adj (study or studies)).tw. or (follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or (epidemiologic* adj (study or studies)).tw. or (cross sectional adj (study or studies)).tw. or Case control.tw. or Cohort analy*.tw. or Longitudinal.tw. or Retrospective.tw. or Cross sectional.tw. or exp epidemiology/	7522780
#96	(Single-arm or "single arm" or non-comparative or "non comparative" or nonRCT or non-RCT or "non RCT" or "no random*" or "not random*" or	10519489

No.	Query	Results
	"non random*" or "non-random*").tw. or exp comparative study/ or cohort.mp. or compared.mp. or groups.mp. or multivariate.mp.	
#97	94 or 95 or 96	15225907
#98	3 and 93 and 97	5700
#99	(editorial or letter or comment or note or "case reports").pt. or "case report*".ti.	3429554
#100	exp animal/ not (exp animal/ and exp human/)	5198266
#101	99 or 100	8556820
#102	98 not 101	5359

Table 81 Search strategy for CCTR and CDSR

No.	Query	Results
#1	exp Gastrointestinal Stromal Tumors/	212
#2	("gastrointestinal stromal tumour*" or "gastrointestinal stromal tumor*" or "gastro-intestinal stromal tumour*" or "gastro-intestinal stromal tumor*" or gist).tw.	718
#3	1 or 2	745
#4	(nilotinib or tasigna or "amn-107" or "amn 107" or amn107).tw.	460
#5	(regorafenib or stivarga or resihance or "bay 73 4506" or "bay 73-4506" or "bay 734506" or "bay73 4506" or "bay73-4506" or bay734506).tw.	640
#6	exp Imatinib Mesylate/	521
#7	(imatinib or gleevac or gleevec or glivec or glivic or ruvise or "cgp 57148" or "cgp-57148*" or cgp57148* or "signal transduction inhibitor 571" or "st 1571" or st1571 or "sti 571" or "sti-571" or sti571 or "st-1571" or "220127-57-1" or "8a1o1m485b" or "bkj8m8g5hi" or "aer 901" or "aer901" or "av 101" or "av101" or egitinib or glipox or imagerolan or imakrebin or imanivec or imaniver or imarem or imatek or imatenil or imatilek or impentri or itivas or latib or leutipol or leuzek or meaxin or nibix or plivatinib or "qti 571" or "qti571" or vianib or "vr 325" or "vr325" or "yd 312" or "yd312").tw.	1625
#8	exp Sorafenib/	625
#9	(sorafenib or nexavar or "bay 43 9006" or "bay 43-9006" or "bay 439006" or "bay43 9006" or "bay43-9006" or bay439006 or "bay 54 9085" or "bay	2078

No.	Query	Results
	549085" or "bay54 9085" or bay549085 or fenesa or "hynap-sora" or reniloxa or revamox or rexanib or sorafeb or soratina or weldinin).tw.	
#10	(pazopanib or armala or votrient or "gw 786034*" or "gw-786034*" or "gw 786034x" or gw786034 or gw786034b or gw786034x or "sb 710468" or "sb 710468a" or sb710468 or sb710468a).tw.	621
#11	(olaratumab or lartruvo or "imc 3g3" or imc3g3 or "ly 3012207" or ly3012207 or "ly-3012207").tw.	63
#12	(dovitinib or "chir 258" or chir258 or "chir-258" or "tki 258" or tki258 or "tki-258").tw.	42
#13	exp Dasatinib/	144
#14	(dasatinib or sprycel or uxil or "bms 354825*" or "bms-354825*" or "bms 354825 03" or "bms 354825-03" or "bms 35482503" or bms354825 or "bms354825 03" or "bms354825-03" or bms35482503).tw.	502
#15	(pexidartinib or turalio or "cml 261" or cml261 or "fp 113" or fp113 or "plexxikon 3397" or plexxikon3397 or "plx 3397" or plx3397 or "plx-3397").tw.	26
#16	(vismodegib or erivedge or "gdc 0449" or "gdc-0449" or gdc0449 or "Hhantag 691" or Hhantag691 or "rg 3616" or rg3616).tw.	109
#17	exp panobinostat/	33
#18	(panobinostat or farydak or "lbh 589" or "lbh 589a" or "lbh 589b" or lbh589 or lbh589a or lbh589b or "mtx 110" or matx110 or "nvp lbh 589" or "nvp lbh589").tw.	120
#19	(buparlisib or "bkm 120*" or "bkm-120*" or "bkm 120 aaa" or "bkm 120 nx" or "bkm 120aaa" or "bkm 120nx" or bkm120 or "bkm120 aaa" or "bkm120 nx" or bkm120aaa or bkm120nx or "nvp bkm 120" or "nvp bkm120").tw.	85
#20	(alpelisib or pigray or vijoice or "byl 719" or "byl-719" or byl719 or "nvp byl 719" or "nvp byl719").tw.	137
#21	(luminespib or "auy 922" or "auy-922" or auy922 or "nvp auy 922" or "nvp auy 922 agb" or "nvp auy 922 nx" or "nvp auy922" or "nvp auy922 agb" or "nvp auy922 nx" or "ver 52296" or ver52296).tw.	10
#22	(onalespib or "at 13387*" or "at-13387*" or "at 13387a" or "at 13387au" or "at 13387x" or at13387 or at13387a or at13387au or at13387x).tw.	10
#23	(ganetespib or "sta 9090" or sta9090 or "sta-9090").tw.	39
#24	exp Everolimus/	1761

No.	Query	Results
#25	(everolimus or affinitor or afinitor or certican or votubia or zortress or "nvp rad 001" or "nvp rad001" or "rad 001*" or "rad-001*" or "rad 001a" or rad001 or rad001a or "sdz rad" or rad666).tw.	3940
#26	exp nivolumab/	755
#27	(nivolumab or opdivo or "bms 936558" or "bms-936558" or bms936558 or "cmab 819" or "cmab-819" or cmab819 or "mdx 1106" or mdx1106 or "ono 4538" or ono4538).tw.	2771
#28	exp Ipilimumab/	379
#29	(ipilimumab or strentarga or yervoy or "bms-734016" or "bms 734016" or "cs 1002" or cs1002 or "ibi 310" or ibi310 or bms734016 or "mdx 010" or "mdx-010" or "mdx 101" or mdx010 or mdx101).tw.	1743
#30	(masitinib or alsitek or kinaction or masatinib or masican or masipro or masivet or masiviera or "ab 1010" or "ab-1010" or ab1010).tw.	115
#31	exp Temozolomide/	561
#32	(temozolomide or temcad or temodal or temodar or temodex or temodol or temomedac or temoxol or methazolastone or kimozo or "ccrg 81045" or "ccrg-81045" or ccrg81045 or "m and b 39831" or "m b 39831" or "mb 39831" or mb39831 or "mk 7365" or mk7365 or "nsc 362856" or "nsc-362856" or nsc362856 or "orp 005" or orp005 or "rp 46161" or rp46161 or "sch 052365" or "sch 52365" or sch052365 or "si 053" or si053).tw.	1654
#33	(binimetinib or balimek or mektovi or "arry 162" or "arry-162" or "arry 438162" or arry162 or arry438162 or "mek 162" or mek162 or "mek-162" or "ono 7703" or ono7703 or "pf 06811462" or "pf 6811462" or pf06811462 or pf6811462).tw.	158
#34	(motesanib or "amg 706" or "amg-706" or amg706).tw.	39
#35	(infigratinib or truseltig or "bbp 831" or bbp831 or "bgj 398" or bgj398 or "nvp bgj 398" or "nvp bgj398").tw.	25
#36	exp sunitinib/	421
#37	(sunitinib or sutent or "pha 2909040ad" or pha2909040ad or "su 010398" or "su 011248" or "su 10398" or "su 11248" or su010398 or su011248 or su10398 or su11248 or "suo 11248" or suo11248 or "gb 102" or gb102).tw.	1379
#38	(avapritinib or "blu 285" or "blu-285" or blu285 or "70c366" or ayvakit or ayvakyt* or "blu 112317" or "blu112317" or "c 366" or "c366" or "cs 3007" or "cs3007" or "x 720776" or "x720776").tw.	39
#39	(ripretinib or ginlock or dcc2618 or "dcc 2618").tw.	41

No.	Query	Results
#40	(cediranib or recentin or zemfirza or "azd 2171" or "azd-2171" or azd2171).tw.	235
#41	(cabozantinib or cometriq or cabometyx or "bms 907351" or "bms-907351" or bms907351 or "xl 184" or xl184).tw.	507
#42	(ponatinib or iclusig or "ap 24534" or "ap-24534" or ap24534).tw.	108
#43	(linsitinib or "osi 906" or "osi 906aa" or "osi-906" or osi906 or osi906aa).tw.	23
#44	(vandetinib or zactima or caprelsa or zictifa or "azd 6474" or "azd-6474" or azd6474 or "zd 6474" or zd6474 or "zd-6474" or "sar 390530" or sar390530).tw.	92
#45	(vatalanib or nublox or "cgp 79787" or "cgp 79787d" or "cgp-79787" or cgp79787 or cgp79787d or "ptk 787" or ptk787 or "ptk-787" or "zk 222584" or zk222584).tw.	41
#46	(crenolanib or "aro 002" or "aro 002 26" or "aro 002-26" or "aro-002" or aro002 or "aro002 26" or "aro002-26" or "cp 868596" or "cp 868596 26" or "cp 868596-26" or cp868596 or "cp868596 26" or "cp868596-26").tw.	28
#47	(amcasertib or "bbi 503" or bbi503 or "bbi-503").tw.	3
#48	(palbociclib or ibrance or "pd 0332991" or "pd 0332991 0054" or "pd 0332991-0054" or "pd 332991" or pd0332991 or "pd0332991 0054" or "pd0332991-0054" or pd332991 or "pf 00080665 73" or "pf 00080665-73" or "pf00080665 73" or "pf00080665-73").tw.	572
#49	(pembrolizumab or keytruda or lambrolizumab or "mk 3475" or mk3475 or "sch 900475" or sch900475).tw.	2783
#50	exp paclitaxel/ or exp albumin-bound paclitaxel/	4492
#51	(paclitaxel or "albumin bound paclitaxel" or "albumin-bound paclitaxel" or "nab paclitaxel" or "nanoparticle albumin bound paclitaxel" or abraxane or abraxus or anzatax or apealea or asotax or biotax or bristaxol or britaxol or coroxane or "endotag-1" or formoxol or genexol or "genexol pm" or hunxol or ifaxol or infinnium or intaxel or liporaxel or medixel or mitotax or nanopac or nanotax or oncogel or onxol or pacitaxel or "paclitaxel nab" or pacxel or padexol or parexel or paxceed or paxene or paxus or pazenir or praxel or taxocris or taxol or taycovit or yewtaxan or "abi 007" or abi007 or "bms 181339" or bms181339 or "bmy 45622" or bmy45622 or "dhp 107" or dhp107 or "dts 301" or dts301 or "fid 007" or fid007 or "mbt 0206" or mbt0206 or "nk 105" or nk105 or "nsc 125973" or "nsc 673089" or nsc125973 or nsc673089 or "oas pac 100" or oaspac100 or "sb 05" or sb05).tw.	11317

No.	Query	Results
#52	(dabrafenib or tafinlar or "drb 436" or drb436 or "gsk 2118436" or "gsk 2118436a" or "gsk 2118436b" or gsk2118436 or gsk2118436a or gsk2118436b).tw.	287
#53	(trametinib or mekinist or "gsk 1120212" or "gsk 1120212b" or gsk1120212 or gsk1120212b or "jtp 74057" or jtp74057 or "snr 1611" or snr1611 or "tmt 212" or tmt212).tw.	352
#54	(amuvatinib or bez235 or "bez 235" or "bez-235" or "hpk 56" or hpk56 or "mp 470" or mp470).tw.	26
#55	(retaspimycin or tanespimycin or "ipi 504" or "ipi-504" or ipi504).tw.	15
#56	(xl820 or "xl 820" or "xl-820").tw.	1
#57	(hqp1351 or "hqp-1351" or "hqp 1351").tw.	6
#58	(tidutamab or xmab18087 or "xmab 18087").tw.	0
#59	("dp-3636" or "dp 3636" or dp3636 or "dp-4444" or "dp 4444" or dp4444 or "dp 4851" or "dp-4851" or dp4854 or "biib 021" or biib021 or lor628 or "lor 628" or "lor-628" or "dp 2976" or dp2976).tw.	4
#60	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59	30215
#61	3 and 60	453
#62	CDSR	3
#63	CCTR	450

Table 82 Search strategy for DARE and HTA

No.	Query	Results
#1	exp Gastrointestinal Stromal Tumors/	212
#2	("gastrointestinal stromal tumour*" or "gastrointestinal stromal tumor*" or "gastro-intestinal stromal tumour*" or "gastro-intestinal stromal tumor*" or gist).tw.	718
#3	1 or 2	745

Table 83 Search strategy for CDR

No.	Query	Results
#1	(gastrointestinal or gastro-intestinal) and stromal	55

H.1.2 Systematic selection of studies

All SLR search algorithms were generated using population, interventions/comparators, outcomes, study design, and time period (PICOS-T)-related elements outlined in Table 84 below. These were generated from the research question pertinent to each section.

Bibliographies of additional, published, relevant systematic review articles were examined to obtain references. Bibliographies of accepted studies were reviewed to obtain further relevant references.

In the first pass, each abstract was reviewed by two independent investigators as to its suitability for inclusion in the study according to the above-defined selection criteria. Discrepancies were resolved by a third investigator. For abstracts that were deemed relevant during the first-level review, full-text articles were retrieved and reviewed.

In the second pass, the full-text version of each publication accepted in the first pass was reviewed by one investigator. All publications rejected at this stage were reviewed by a second investigator to confirm the rejection decision. For each excluded study, a specific reason for exclusion was provided and by a second investigator. A third investigator was consulted to resolve disagreements where necessary.

Data extraction was performed in the following steps:

1. Information from the full-text articles was extracted independently into data extraction forms by one investigator.
2. Data extraction was independently validated by a second investigator; a third investigator was consulted to resolve disagreements as necessary.

Publications reporting duplicate results were not extracted into the data extraction table.

Table 84 Inclusion and exclusion criteria for used for assessment studies

PICOS-T	Inclusion criteria	Exclusion criteria	Inclusion criteria	Exclusion criteria
	Global SLR		Danish adaption	
Population	Adult (age ≥18 years) patients with unresectable GIST and with the PDGFRA D842V mutation	• Healthy volunteers • Paediatric population	Unchanged	

	regardless of previous therapy	• Disease other than PDGFRA D842V mutation		
Intervention	All approved or investigational pharmacological interventions used for the treatments of GIST: • Alpelisib • Amcasertib • Amuvatinib • Avapritinib • Binimetinib • Buparlisib • Cabozantinib • Cediranib • Crenolanib • Dabrafenib • Dasatinib • Dovitinib • Everolimus • Ganetespib • Imatinib • Infigratinib • Ipilimumab • Linsitinib • Luminespib • Masitinib • Motesanib • Nilotinib • Nivolumab • Olaratumab • Onalespib • Paclitaxel • Palbociclib • Panobinostat • Pazopanib	Non-pharmacological interventions	All approved or investigational pharmacological interventions used for the treatments of GIST in Denmark: • Imatinib • Sunitinib • Regorafenib • Avapritinib (intervention)	• Non-pharmacological interventions • Alpelisib • Amcasertib • Amuvatinib • Binimetinib • Buparlisib • Cabozantinib • Cediranib • Crenolanib • Dabrafenib • Dasatinib • Dovitinib • Everolimus • Ganetespib • Infigratinib • Ipilimumab • Linsitinib • Luminespib • Masitinib • Motesanib • Nilotinib • Nivolumab • Olaratumab • Onalespib • Paclitaxel • Palbociclib • Panobinostat • Pazopanib • Pembrolizumab • Pexidartinib • Ponatinib

	• Pembrolizumab • Pexidartinib • Ponatinib • Regorafenib • Retaspimycin • Ripretinib • Sunitinib • Temozolomide • Trametinib • Vandetanib • Vatalanib • Vismodegib • Other investigational therapies - xl820, hqp1351, xmab18087, bbi 503, bez235, dp3636, dp4444, dp4854, dp4851, biib021, dp2976, lor628		• Retaspimycin • Ripretinib • Temozolomide • Trametinib • Vandetanib • Vatalanib • Vismodegib Other investigational therapies - xl820, hqp1351, xmab18087, bbi 503, bez235, dp3636, dp4444, dp4854, dp4851, biib021, dp2976, lor628
Comparators	• Placebo • Best supportive care (author defined) • Any other pharmacological/non-pharmacological intervention • No comparator limit for single-arm trials	None	Unchanged
Outcomes	• Response rate • Overall survival	Not reporting any of the outcomes included in the list	Unchanged

	• Progression-free survival • Adverse events • Study/ treatment discontinuation		
Study design	• Randomised controlled trials (RCTs) • Non-randomised controlled trials (nRCTs) • Single-arm trials • Retrospective and prospective cohort studies • Real-world evidence studies • Systematic reviews*	• Letters, comments, and editorials • Case series or case reports	Unchanged
Language	No limits	None	Unchanged
Countries	No limits	None	Unchanged
Time limit	No limits	None	Unchanged

Abbreviation: GIST, gastrointestinal stromal tumour; ORR, overall response rate; PDGFRA, platelet-derived growth factor receptor alpha

Note: * Systematic reviews will be included and flagged for bibliography searches. ^List is not exhaustive. A detailed extraction grid will be prepared before the data extraction stage and will be finalised after alignment as per the requirements

The PRISMA flow diagram of the clinical SLR is presented in Figure 57 below. Among the 7504 publications initially identified and screened from multiple databases, 7020 were excluded, leaving 484 publications for further evaluation of eligibility. 20 studies could not be retrieved during the full-text screening. Of the remaining 464 publications, 422 publications were excluded during full-text screening. Therefore, 42 publications were included into the report, which included 25 unique studies.

From these studies, 4 were considered most appropriate to inform the Danish submission dossier. The remaining studies either had a comparator that is not used in Denmark or had

very small PDGFRA D842V population sizes, most of which did not report outcomes of interest as well.

The included studies are:

- NAVIGATOR study, which is most relevant for this patient population to inform on the efficacy of avapritinib; available as CSR (51) and publication (60)
- BLU-285-1002 study, which is the most relevant to inform the comparative effectiveness of avapritinib vs TKI therapy, as it provides the most complete data set that is currently available for this patient population and will form the basis for the indirect treatment comparison; available as an abstract (61)
- Von Mehren et al., 2021, the which is most relevant for the indirect treatment comparison of NAVIGATOR and BLU-285-1002 for this population group; available as a study report (5) and as a publication (62)
- Cassier et al., 2012 does not form part of the main efficacy data for this submission and is purely used as a scenario analysis to the indirect treatment comparison and is described in Appendix C.1.5 and. Outcomes from the BLU-285-1002 IPW are naively compared against Cassier et al., 2012 to provide face validity on the robustness of the BLU-285-1002 results. Available as a publication (3)

The details of the included studies from the clinical SLR are provided in Table 85 below.

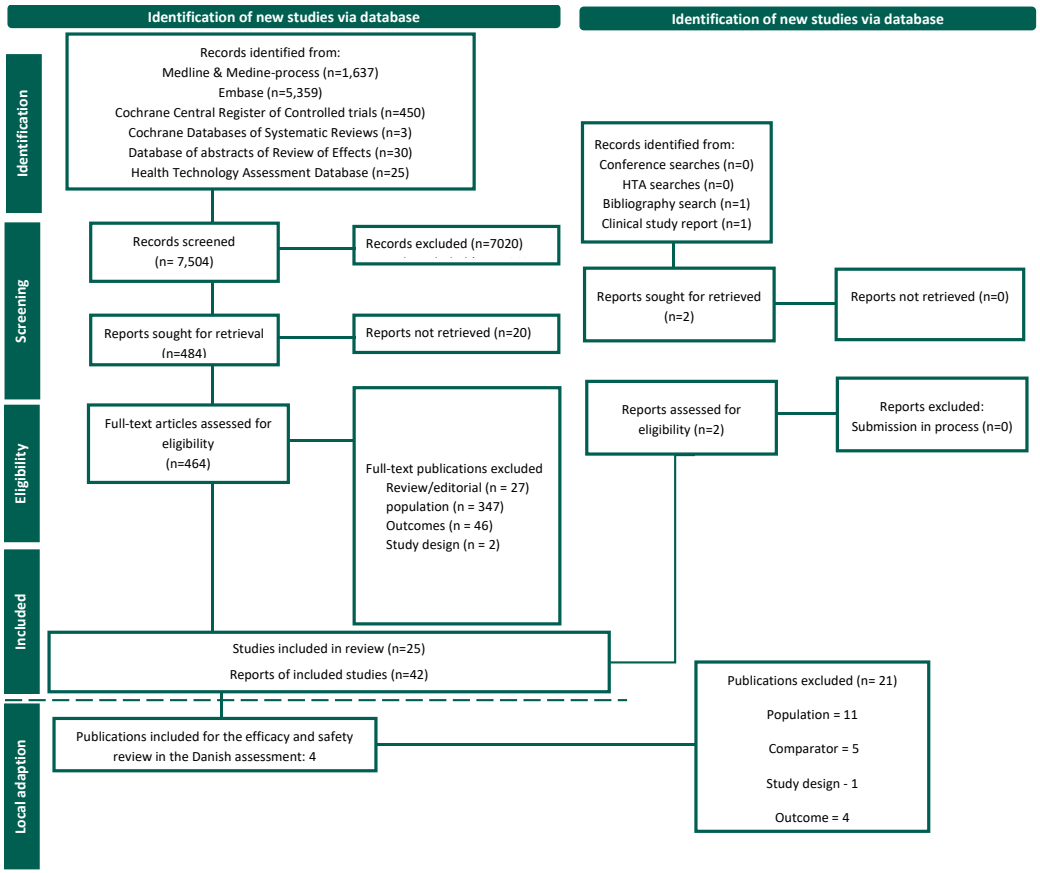

Figure 57 Clinical PRISMA flow diagram

H.1.2.1 Included studies

Table 85 Overview of study design for studies included in the technology assessment

Study/ID	Aim	Study design	Patient population	Intervention and comparator	Primary outcome and follow-up period	Secondary outcome and follow-up period
Non-randomised controlled trials and observational studies						
Von Mehren et al., 2018 **BLU-285-1002**	To characterize response and survival of patients with PDGFRα D842 mutant GIST treated with currently approved TKIs.	Multicenter, retrospective study	Patients with locally advanced, metastatic, or recurrent PDGFRA D842V mutant GIST previously treated with a tyrosine kinase inhibitor (n=22)	Imatinib (n=21), Sunitinib (n=15), Dasatinib (n=8), Regorafenib (n=4), Nilotinib (n=2), Pazopanib (n=1)	NR	Overall survival, best response rate, duration of response and progression-free survival (follow up period: NR)
Von Mehren et al., 2021	To compare efficacy of avapritinib in patients enrolled in the NAVIGATOR phase 1 trial (NCT02508532) with the efficacy of other tyrosine kinase inhibitors (TKIs) in patients with unresectable/metastatic PDGFRA D842V-	Retrospective, indirect analysis of NAVIGATOR phase 1 trial and Study 1002 real-world study	Unresectable/metastatic GIST harboring a PDGFRA D842V mutation (n = 75; 56 patients in NAVIGATOR and 19 patients in study 1002))	Avapritinib (n = 56) Other tyrosine kinase inhibitors (n = 19)	Progression- free survival (follow up period: NR)	NR

Study/ID	Aim	Study design	Patient population	Intervention and comparator	Primary outcome and follow-up period	Secondary outcome and follow-up period
	mutant GIST enrolled in a retrospective natural history study (Study 1002)					
Cassier et al., 2012	Outcome of patients with platelet-derived growth factor receptor alpha-mutated gastrointestinal stromal tumors in the tyrosine kinase inhibitor era	Retrospective survey	Patients with advanced PDGFRA-mutant GISTs (n = 58) -- PDGFRA D842V mutation population (n = 32)	Imatinib (n = 32)	NR	Response rate, overall survival and progression-free survival Note: All above outcomes reported for PGDFRA D842V mutation patients
BLU-285-1101 **NAVIGATOR**	To present a comprehensive description of the efficacy and safety of avapritinib in adult patients with unresectable or metastatic GIST.	Open-label, single arm, multicenter, two parts, phase I trial	Unresectable or metastatic GIST patients (n = 250) -- PDGFRA D842V mutation population (n = 56)	Avapritinib (n = 56)	Duration of response, time to response, progression-free survival, overall survival, clinical benefit rate, antitumor activity as measured by Choi criteria, mutational changes in KIT, PDGFRA, and other cancer relevant genes in tumor tissue at baseline and at the	Overall survival and changes in KIT, PDGFRA, and other cancer relevant gene mutant allele fractions with antitumor activity

Study/ID	Aim	Study design	Patient population	Intervention and comparator	Primary outcome and follow-up period	Secondary outcome and follow-up period
					end of treatment and in ctDNA at baseline and the biologic activity of avapritinib Note: Duration of response, time to response, progression-free survival, overall survival, clinical benefit rate reported for PGDFRA D842V mutation patients	

H.1.2.2 Excluded studies

Table 86 provides an overview of the publications excluded with reasons.

Table 86 Overview of publications excluded at full-text screening from the clinical SLR

Publication	Exclusion reason
To evaluate tumor response to olaratumab in previously treated patients with metastatic gastrointestinal stromal tumor with or without PDGFRa mutations (cohorts 1 and 2, respectively)	Comparator
To identify factors related to progression-free and overall survival of patients starting imatinib therapy as well as to attempt to identify the factors related to subgroup of patients with the longterm survival	Outcome
To analyze a large series of neurofibromatosis type 1-related GISTs to discuss the therapeutic implications.	Study design
To evaluate efficacy of the targeted chemotherapy in advanced gastrointestinal stromal tumours with non-exon 11 KIT mutations	Population
To analyze the outcomes and factors predicting results of sunitinib therapy in inoperable/metastatic CD117(+) GIST patients after imatinib failure	Population
To analyze the clinical beneft of 2L sunitinib and 3L regorafenib treatment in advanced GIST OS using real-world evidence from patient-reported outcomes	Outcome
To assess the efficacy and safety of sunitinib with regards to primary genotypes of tumor in Korean patients with advanced gastrointestinal stromal tumors (GISTs) who failed an initial therapy of imatinib.	Population
To assess sorafenib in three patients with a PDGFRA-D842V mutated metastatic GIST.	Outcome
To evaluate the impact of primary and secondary kinase genotype on sunitinib activity.	Outcome
To assess imatinib resumption among metastatic Italian GIST patients after progression to conevntional TKIs.	Population
To assess the efficacy of imatinib for different tumor genotypes in Korean patients with advanced gastrointestinal stromal tumors (GIST).	Population
To retrospectively analyze the efficacy of first-line imatinib in patients with advanced GISTs harboring PDGFRA mutations.	Population

To evaluate the safety and the antineoplastic activity of avapritinib in Chinese patients with unresectable/metastatic gastrointestinal stromal tumors (GIST)	Population
To assess the antitumour activity and safety of dovitinib in patients with GIST refractory or intolerant to imatinib in the second-line setting.	Population
To evaluate safety and antitumor efficacy of crenolanib in advanced GIST with PDGFRA D842V mutations	Comparator
To evaluate the 6-month progression-free survival, tumor objective response, and overall survival rates in patients with GISTs treated with dasatinib.	Comparator
To evaluate the efficacy and safety of dasatinib in the third-line treatment of metastatic gastrointestinal stromal tumors (GIST).	Comparator
To evaluate tumor response to olaratumab in previously treated patients with metastatic gastrointestinal stromal tumor with or without PDGFRa mutations (cohorts 1 and 2, respectively)	Comparator
To examine relationship between mutations in kinases and clinical response to imatinib in a group of patients with advanced GISTs.	Population
To examine the correlation between kinase genotype, imatinib dose, and clinical outcomes in 397 patients with GIST from the North American phase III trial.	Population
To evaluate efficacy and safety of avapritinib versus regorafenib as third-line or later treatment in patients with unresectable or metastatic gastro-intestinal stromal tumors .	Population
[Clinical analysis of efficacy and prognosis of intermediate risk gastric stromal tumor patients]. [Chinese]	Population
[Effectiveness and safety of imatinib in seven gastrointestinal stromal tumor cases]. [Spanish]	Population
[Gastrointestinal stromal tumors. Analysis of 40 cases]. [Spanish]	Population
[Imatinib mesylate alone for refractory advanced gastrointestinal stromal tumor]. [Chinese]	Population
[Imatinib mesylate in the treatment of advanced gastrointestinal stromal tumors]. [Chinese]	Population
[Role of FDG PET in the staging, recurrence and treatment response to imatinib (Glivec) in patients with gastrointestinal stromal tumors]. [Spanish]	Population

[Study on the usage, effectiveness, and toxicity associated to treatment with sorafenib]. [Spanish]	Population
18FDG-Positron emission tomography for the early prediction of response in advanced soft tissue sarcoma treated with imatinib mesylate (Glivec).	Population
A clinical study on GIST in Babylon.	Population
A dose-escalating phase i of imatinib mesylate with fixed dose of metronomic cyclophosphamide in targeted olid tumours.	Population
A first in human, safety, pharmacokinetics, and clinical activity phase I study of once weekly administration of the Hsp90 inhibitor ganetespib (STA-9090) in patients with solid malignancies.	Population
A lower dosage of imatinib in patients with gastrointestinal stromal tumors with toxicity of the treatment.	Population
A multicenter long-term study of imatinib treatment for Japanese patients with unresectable or recurrent gastrointestinal stromal tumors.	Population
A multicenter phase II study of nivolumab +/- ipilimumab for patients with metastatic sarcoma (Alliance A091401): results of expansion cohorts	Population
A multicenter phase II study of pazopanib in patients with advanced gastrointestinal stromal tumors (GIST) following failure of at least imatinib and sunitinib.	Population
A multicenter, dose-finding, phase 1b study of imatinib in combination with alpelisib as third-line treatment in patients with advanced gastrointestinal stromal tumor.	Population
A mutation-specific, single-arm, phase 2 study of dovitinib in patients with advanced malignancies	Population
A nomogram predicting progression free survival in patients with gastrointestinal stromal tumor receiving sunitinib: Incorporating pre-treatment and post-treatment parameters.	Population
A patient's perspective on the side effects of tyrosine kinase inhibitors in the treatment of advanced and metastatic gastrointestinal stromal tumors.	Population
A Phase 2 Study of the Hsp90 Inhibitor AUY922 as Treatment for Patients with Refractory Gastrointestinal Stromal Tumors.	Population
A Phase I Study of Binimetinib (MEK162) Combined with Pexidartinib (PLX3397) in Patients with Advanced Gastrointestinal Stromal Tumor.	Population

A phase I study of single-agent nilotinib or in combination with imatinib in patients with imatinib-resistant gastrointestinal stromal tumors	Population
A phase I study of the HSP90 inhibitor retaspimycin hydrochloride (IPI-504) in patients with gastrointestinal stromal tumors or soft-tissue sarcomas.	Population
A phase Ib study of BGJ398 in combination with imatinib in patients with advanced gastrointestinal stromal tumor (GIST).	Population
A phase Ib study of BGJ398, a pan-FGFR kinase inhibitor in combination with imatinib in patients with advanced gastrointestinal stromal tumor.	Population
A phase II trial of temozolomide as a 6-week, continuous, oral schedule in patients with advanced soft tissue sarcoma: a study by the Spanish Group for Research on Sarcomas.	Population
A Phase II trial of vandetanib in children and adults with succinate dehydrogenase-deficient gastrointestinal stromal tumor.	Population
A phase I-II study of everolimus (RAD001) in combination with imatinib in patients with imatinib-resistant gastrointestinal stromal tumors.	Population
A pilot study of imatinib mesylate (STI571) on gastrointestinal stromal tumors in Japanese patients.	Population
A prospective, multicenter, phase 2 study of imatinib mesylate in korean patients with metastatic or unresectable gastrointestinal stromal tumor.	Population
A randomised phase 2 study of continuous or intermittent dosing schedule of imatinib re-challenge in patients with tyrosine kinase inhibitor-refractory gastrointestinal stromal tumours.	Population
A Randomized Phase II Study of Nivolumab Monotherapy or Nivolumab Combined with Ipilimumab in Patients with Advanced Gastrointestinal Stromal Tumors	Population
A randomized phase II study of perifosine (P) plus imatinib for patients with imatinib-resistant gastrointestinal stromal tumor (GIST)	Population
A systematic review and network meta-analysis of post-imatinib therapy in advanced gastrointestinal stromal tumour.	Review/editorial
A systematic review and network meta-analysis of the efficacy and safety of third-line and over third-line	Review/editorial

therapy after imatinib and TKI resistance in advanced gastrointestinal stromal tumor.	
A two-arm phase II study of temozolomide in patients with advanced gastrointestinal stromal tumors and other soft tissue sarcomas.	Population
Absence of progression as assessed by response evaluation criteria in solid tumors predicts survival in advanced GI stromal tumors treated with imatinib mesylate: the intergroup EORTC-ISG-AGITG phase III trial	Population
Activity and Safety of Palbociclib in Patients with Advanced Gastrointestinal Stromal Tumors Refractory to Imatinib and Sunitinib: A Biomarker-driven Phase 2 study.	Population
Activity and safety of the multi-target tyrosine kinase inhibitor cabozantinib in patients with metastatic gastrointestinal stromal tumour after treatment with imatinib and sunitinib: European Organisation for Research and Treatment of Cancer phase II trial 1317 'CaboGIST'.	Population
Activity and side effects of imatinib in patients with gastrointestinal stromal tumors: data from a German multicenter trial.	Population
Adherence to the guidelines and the pathological diagnosis of high-risk gastrointestinal stromal tumors in the real world.	Population
Advanced gastrointestinal stromal tumor patients benefit from palliative surgery after tyrosine kinase inhibitors therapy.	Population
Advanced gastrointestinal stromal tumor patients with complete response after treatment with imatinib mesylate.	Population
Adverse reactions of sorafenib, sunitinib, and imatinib in treating digestive system tumors.	Population
An updated overall survival analysis with correction for protocol-planned crossover of the international, phase III, randomized, placebo-controlled trial of regorafenib in advanced gastrointestinal stromal tumors after failure of imatinib and sunitinib (GRID).	Population
An updated overall survival analysis with correction for protocol-planned crossover of the international, phase III, randomized, placebo-controlled trial of regorafenib in advanced gastrointestinal stromal tumors after failure of imatinib and sunitinib (GRID).	Population
An updated overall survival analysis with correction for protocol-planned crossover of the international, phase	Population

III, randomized, placebo-controlled trial of regorafenib in advanced gastrointestinal stromal tumors after failure of imatinib and sunitinib (GRID).	
Analysis of serum protein biomarkers and circulating tumor (ct) DNA for activity of dovitinib in patients (pts) with tyrosine kinase inhibitor (TKI)-refractory gastrointestinal stromal tumors (GIST).	Population
Analysis of serum protein biomarkers, circulating tumor DNA, and dovitinib activity in patients with tyrosine kinase inhibitor-refractory gastrointestinal stromal tumors	Population
Approval summary: imatinib mesylate in the treatment of metastatic and/or unresectable malignant gastrointestinal stromal tumors	Population
Approval summary: imatinib mesylate in the treatment of metastatic and/or unresectable malignant gastrointestinal stromal tumors	Population
Approval summary: sunitinib for the treatment of imatinib refractory or intolerant gastrointestinal stromal tumors and advanced renal cell carcinoma	Population
Assessment of Adherence to Imatinib and Health-Related Quality of Life Among Patients with Gastrointestinal Stromal Tumor: A Cross-Sectional Study in an Oncology Clinic in Malaysia.	Population
Assessment of early response to imatinib 800 mg after 400 mg progression by 18F-fluorodeoxyglucose PET in patients with metastatic gastrointestinal stromal tumors.	Population
Assessment of gastrointestinal stromal tumors with computed tomography following treatment with imatinib mesylate.	Population
Association of ABCG2 polymorphism with clinical efficacy of imatinib in patients with gastrointestinal stromal tumor.	Outcome
Association of Combination of Conformation-Specific KIT Inhibitors With Clinical Benefit in Patients With Refractory Gastrointestinal Stromal Tumors: A Phase 1b/2a Nonrandomized Clinical Trial.	Population
Association of intratumoral vascular endothelial growth factor expression and clinical outcome for patients with gastrointestinal stromal tumors treated with imatinib mesylate.	Population
Avapritinib in advanced gastrointestinal stromal tumor: case series and review of the literature from a tertiary care center in India.	Population

Benefit of pazopanib in advanced gastrointestinal stromal tumours: results from a phase II trial (SSG XXI, PAGIST)	Population
Blood neutrophil-to-lymphocyte ratio is associated with prognosis in advanced gastrointestinal stromal tumors treated with imatinib.	Population
Broad spectrum of regorafenib activity on mutant KIT and absence of clonal selection in gastrointestinal stromal tumor (GIST): correlative analysis from the GRID trial.	Population
Cabozantinib for the treatment of solid tumors: a systematic review.	Review/editorial
Caveolin-1 expression predicts favourable outcome and correlates with PDGFRA mutations in gastrointestinal stromal tumours (GISTs).	Population
Characteristics and outcomes of patients with advanced sarcoma enrolled in early phase immunotherapy trials.	Population
Circulating levels of soluble KIT serve as a biomarker for clinical outcome in gastrointestinal stromal tumor patients receiving sunitinib following imatinib failure.	Population
Clinical Activity of Ripretinib in Patients with Advanced Gastrointestinal Stromal Tumor Harboring Heterogeneous KIT/PDGFRA Mutations in the Phase III INVICTUS Study.	Population
Clinical and pathological characteristics and their effect on survival in elderly patients with gastrointestinal stromal tumors.	Population
Clinical Benefit of Ripretinib Dose Escalation After Disease Progression in Advanced Gastrointestinal Stromal Tumor: an Analysis of the INVICTUS Study	Population
Clinical characteristics and treatment outcome in a large multicenter observational cohort of pdgfra exon 18 mutated gastrointestinal stromal tumor (GIST) patients.	Population
Clinical characteristics and treatment outcome in a large multicentre observational cohort of PDGFRA exon 18 mutated gastrointestinal stromal tumour patients.	Population
Clinical effectiveness and cost-effectiveness of imatinib dose escalation for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours that have progressed on treatment at a dose of 400 mg/day: a systematic review and economic evaluation. [Review]	Review/editorial

Clinical efficacy and safety of sunitinib after imatinib failure in Japanese patients with gastrointestinal stromal tumor.	Population
Clinical efficacy of second-generation tyrosine kinase inhibitors in imatinib-resistant gastrointestinal stromal tumors: a meta-analysis of recent clinical trials.	Review/editorial
Clinical evaluation of continuous daily dosing of sunitinib malate in patients with advanced gastrointestinal stromal tumour after imatinib failure	Population
Clinical outcome in gastrointestinal stromal tumor patients who interrupted imatinib after achieving stable disease or better response.	Population
Clinical outcomes of imatinib dose escalation versus sunitinib in first-line imatinib-failure gastrointestinal stromal tumour.	Population
Clinical outcomes of patients with advanced gastrointestinal stromal tumors: safety and efficacy in a worldwide treatment-use trial of sunitinib.	Population
Clinical outcomes of patients with gastrointestinal stromal tumor in phase I clinical trials.	Population
Clinical practice and outcomes in advanced gastrointestinal stromal tumor: Experience from an Indian tertiary care center.	Population
Clinicopathological and Molecular Characterization of Metastatic Gastrointestinal Stromal Tumors with Prolonged Benefit to Frontline Imatinib.	Population
Clinicopathological and therapeutic analysis of PDGFRA mutated gastrointestinal stromal tumor.	Population
Combined KIT and CTLA-4 Blockade in Patients with Refractory GIST and Other Advanced Sarcomas: A Phase Ib Study of Dasatinib plus Ipilimumab.	Population
Comparative Efficacy and Safety of Different Regimens of Advanced Gastrointestinal Stromal Tumors After Failure Prior Tyrosine Kinase Inhibitors: A Network Meta-Analysis.	Review/editorial
Comparative risk assessment of imatinib, nilotinib and dasatinib in randomized controlled trials: A meta-analysis.	Review/editorial
Comparison of Dasatinib- and Imatinib-Related Cardiotoxic Adverse Events in Japanese Patients With Chronic Myeloid Leukemia and Gastrointestinal Stromal Tumor.	Population

Comparison of performance of various tumor response criteria in assessment of sunitinib activity in advanced gastrointestinal stromal tumors.	Population
Comparison of two doses of imatinib for the treatment of unresectable or metastatic gastrointestinal stromal tumors: a meta-analysis of 1,640 patients.	Review/editorial
Compassionate Use of Ripretinib for Patients With Metastatic Gastrointestinal Stromal Tumors: Taiwan and Hong Kong Experience.	Population
Complete longitudinal analyses of the randomized, placebo-controlled, phase III trial of sunitinib in patients with gastrointestinal stromal tumor following imatinib failure	Population
Continuous daily dosing (CDD) of sunitinib (SU) in pts with advanced GIST: updated efficacy, safety, PK and pharmacodynamic analysis	Population
Continuous vs intermittent imatinib treatment in advanced GIST after one year: a prospective randomized phase III trial of the French Sarcoma Group	Population
Correction to Lancet Oncol 2020; 21: 923-34 (The Lancet Oncology (2020) 21(7) (923-934), (S1470204520301686), (10.1016/S1470-2045(20)30168-6)).	Review/editorial
Correlation of immunophenotype with progression-free survival in patients with gastrointestinal stromal tumors treated with imatinib mesylate.	Population
Correlation of long-term results of imatinib in advanced gastrointestinal stromal tumors with next-generation sequencing results: analysis of phase 3 SWOG intergroup trial S0033	Population
Development of hypogammaglobulinemia in patients treated with imatinib for chronic myeloid leukemia or gastrointestinal stromal tumor.	Population
Different factors are responsible for predicting relapses after primary tumors resection and for imatinib treatment outcomes in gastrointestinal stromal tumors.	Population
Discontinuation of imatinib in patients with advanced gastrointestinal stromal tumours after 3 years of treatment: an open-label multicentre randomised phase 3 trial	Population
Does imatinib turn recurrent and/or metastasized gastrointestinal stromal tumors into a chronic disease? - Single center experience.	Population

Does immunohistochemistry provide additional prognostic data in gastrointestinal stromal tumors?.	Population
Does interruption of imatinib (IM) in responding GIST patients after one year of treatment influence the secondary resistance to IM after its reintroduction? Updated results of the prospective French Sarcoma Group randomized phase III trial on long term survival	Population
Does interruption of imatinib (IM) in responding patients after three years of treatment influence outcome of patients with advanced GIST included in the BFR14 trial	Population
Dose effect of imatinib (IM) in patients (pts) with metastatic GIST - Phase III Sarcoma Group Study S0033	Population
Dose escalation of imatinib after failure of standard dose in Korean patients with metastatic or unresectable gastrointestinal stromal tumor.	Population
Dose-escalation study of a second-generation non-ansamycin HSP90 inhibitor, onalespib (AT13387), in combination with imatinib in patients with metastatic gastrointestinal stromal tumour.	Population
Dutch Gastrointestinal Stromal Tumor (GIST) Registry Data Comparing Sunitinib with Imatinib Dose Escalation in Second-Line Advanced Non-KIT Exon 9 Mutated GIST Patients.	Outcome
Early prediction of response to sunitinib after imatinib failure by 18F-fluorodeoxyglucose positron emission tomography in patients with gastrointestinal stromal tumor	Population
Effect of five years of imatinib on cure for patients with advanced GIST: Updated survival results from the prospective randomized phase III BFR14 trial.	Population
Effect of Regorafenib in Delaying Definitive Deterioration in Health-Related Quality of Life in Patients with Advanced Cancer of Three Different Tumor Types.	Population
Effectiveness and safety of imatinib in seven gastrointestinal stromal tumor cases. [Spanish]	Population
Effi cacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): An international, multicentre, randomised, placebo-controlled, phase 3 trial.	Population
Efficacy and safety evaluation of two doses of imatinib for the treatment of advanced gastrointestinal stromal tumors (GISTs).	Review/editorial

Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors	Population
Efficacy and safety of motesanib, an oral inhibitor of VEGF, PDGF, and Kit receptors, in patients with imatinib-resistant gastrointestinal stromal tumors.	Population
Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial	Population
Efficacy and safety of regorafenib in Japanese patients with advanced gastrointestinal stromal tumors.	Outcome
Efficacy and safety of regorafenib in Korean patients with advanced gastrointestinal stromal tumor after failure of imatinib and sunitinib: a multicenter study based on the management access program	Population
Efficacy and safety of regorafenib in patients with metastatic and/or unresectable GI stromal tumor after failure of imatinib and sunitinib: a multicenter phase II trial.	Population
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.	Population
Efficacy and safety of ripretinib in Chinese patients with advanced gastrointestinal stromal tumors: a real-world, multicenter, observational study.	Population
Efficacy and safety of sunitinib in Chinese patients with imatinib-resistant or -intolerant gastrointestinal stromal tumors.	Population
Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial	Population
Efficacy and safety profile of imatinib mesylate (ST1571) in Japanese patients with advanced gastrointestinal stromal tumors: a phase II study (STI571B1202).	Population
Efficacy evaluation of imatinib in the treatment of patients with gastrointestinal stromal tumors.	Review/editorial
Efficacy evaluation of imatinib treatment in patients with gastrointestinal stromal tumors: a meta-analysis.	Review/editorial
Efficacy evaluation of nilotinib treatment in different genomic subtypes of gastrointestinal stromal tumors: A meta-analysis and systematic review.	Review/editorial

Efficacy of imatinib dose escalation in Chinese gastrointestinal stromal tumor patients.	Population
Efficacy of post-first-line agents for advanced gastrointestinal stromal tumors following imatinib failure: A network meta-analysis.	Review/editorial
Efficacy of sorafenib in patients with gastrointestinal stromal tumors in the third- or fourth-line treatment: A retrospective multicenter experience.	Population
Efficacy of sunitinib in patients with imatinib-resistant gastrointestinal stromal tumors.	Population
Efficacy of sunitinib in Turkish patients with gastrointestinal stromal tumors: Retrospective multicenter experience.	Population
Efficacy, safety, and pharmacokinetics of imatinib dose escalation to 800 mg/day in patients with advanced gastrointestinal stromal tumors.	Outcome
EPIGIST: An observational real-life study on patients with metastatic gastrointestinal stromal tumors receiving imatinib.	Population
Evaluation of self-reported progression and correlation of imatinib dose to survival in patients with metastatic gastrointestinal stromal tumors: an open cohort study.	Population
Exploiting antitumor immunity to overcome relapse and improve remission duration	Population
Exploratory analysis of tumor growth rate in patients with advanced gastrointestinal stromal tumors (GIST) treated with regorafenib in the GRID phase 3 trial	Population
FDA Approval Summary: ripretinib for advanced gastrointestinal stromal tumor	Review/editorial
First-in-human phase I dose escalation study of a second-generation non-ansamycin HSP90 inhibitor, AT13387, in patients with advanced solid tumors.	Population
Fluid retention associated with imatinib treatment in patients with gastrointestinal stromal tumor: quantitative radiologic assessment and implications for management.	Population
Follow-up results after 9 years (yrs) of the ongoing, phase II B2222 trial of imatinib mesylate (IM) in patients (pts) with metastatic or unresectable KIT+ gastrointestinal stromal tumors (GIST).	Population
Fractioned dose regimen of sunitinib for patients with gastrointestinal stromal tumor: A pharmacokinetic and treatment efficacy study.	Outcome

Frequent rectal gastrointestinal stromal tumor recurrences in the imatinib era: Retrospective analysis of an International Patient Registry.	Population
Gastrointestinal stromal tumor (GIST) -- single center experience of prolonged treatment with imatinib	Population
Gastrointestinal Stromal Tumor Patients with Molecular Testing Exhibit Superior Survival Compared to Patients without Testing: Results from the Life Raft Group (LRG) Registry.	Population
Gastrointestinal stromal tumor: 15-years' experience in a single center.	Population
Gastrointestinal stromal tumor: A report of eight cases. [Portuguese]	Population
Gastrointestinal stromal tumors. Analysis of 40 cases. [Spanish]	Population
Gastrointestinal Stromal Tumours (GIST): A Review of Cases from Nigeria.	Review/editorial
Gastrointestinal stromal tumours (GISTs): A descriptive study on 29 cases.	Population
Genomic Subtypes of GISTs for Stratifying Patient Response to Sunitinib following Imatinib Resistance: A Pooled Analysis and Systematic Review.	Study design
Hematologic toxicities of sunitinib in patients with gastrointestinal stromal tumors: a systematic review and meta-analysis.	Review/editorial
Hematological and nonhematological toxicities of imatinib mesylate in patients with chronic myeloid leukemia and gastrointestinal stromal tumor.	Population
Hepatic metastases in gastrointestinal stromal tumors: oncologic outcomes with curative-intent hepatectomy, resection of treatment-resistant disease, and tyrosine kinase inhibitor therapy alone.	Population
Hepatic toxicity during regorafenib treatment in patients with metastatic gastrointestinal stromal tumors.	Population
Imatinib (Glivec) and gastrointestinal stromal tumours in Nigerians.	Population
Imatinib does not induce cardiac left ventricular failure in gastrointestinal stromal tumours patients: Analyis of EORTC-ISG-AGITG study 62005.	Population

Imatinib dose escalation versus sunitinib as a second line treatment in KIT exon 11 mutated GIST: a retrospective analysis.	Population
Imatinib dose escalation versus sunitinib as a second-line treatment against advanced gastrointestinal stromal tumors: A nationwide population-based cohort study.	Population
Imatinib efficacy by tumor genotype in Asian patients with metastatic or recurrent gastrointestinal stromal tumors (GISTs): A retrospective study of Korean GIST Study Group (KGSG).	Outcome
Imatinib escalation or sunitinib treatment after first-line imatinib in metastatic gastrointestinal stromal tumor patients.	Population
Imatinib for the treatment of patients with unresectable and/or metastatic gastrointestinal stromal tumours: Systematic review and economic evaluation.	Review/editorial
Imatinib for the treatment of patients with unresectable or metastatic malignant KIT-positive gastrointestinal stromal tumours: an open-label Belgian trial.	Population
Imatinib in combination with phosphoinositol kinase inhibitor buparlisib in patients with gastrointestinal stromal tumour who failed prior therapy with imatinib and sunitinib: a Phase 1b, multicentre study.	Population
Imatinib in gastrointestinal stromal tumour: Northern Cancer Network experience.	Population
Imatinib mesylate (IM) therapy in elderly patients affected by advanced gastrointestinal stromal tumor (GIST).	Population
Imatinib mesylate (STI-571 Glivec, GleevecTM) is an active agent for gastrointestinal stromal tumours, but does not yield responses in other soft-tissue sarcomas that are unselected for a molecular target: Results from an EORTC Soft Tissue and Bone Sarcoma Group phase II study.	Population
Imatinib mesylate alone for refractory advanced gastrointestinal stromal tumor. [Chinese]	Population
Imatinib Mesylate for Patients With Unresectable or Recurrent Gastrointestinal Stromal Tumors: 10-Year Experience From Vietnam.	Population
Imatinib mesylate for the treatment of gastrointestinal stromal tumours: Best monitored with FDG PET.	Population

Imatinib mesylate in the treatment of advanced gastrointestinal stromal tumors. [Chinese]	Population
Imatinib mesylate therapy in advanced gastrointestinal stromal tumors: Experience from a single institute.	Population
Imatinib plasma levels are correlated with clinical benefit in patients with unresectable/metastatic gastrointestinal stromal tumors.	Population
Imatinib plasma levels in patients with gastrointestinal stromal tumour under routine clinical practice conditions.	Population
Imatinib plus low-dose doxorubicin in patients with advanced gastrointestinal stromal tumors refractory to high-dose imatinib: a phase I-II study by the Spanish Group for Research on Sarcomas.	Population
Imatinib use for gastrointestinal stromal tumors among older patients in Japan and Taiwan.	Population
Imatinib-associated skin rash is related to treatment outcome in patients with unresectable and/or metastatic gastrointestinal stromal tumor.	Population
Imatinib-resistant gastrointestinal stromal tumors in the era of second- and third-line tyrosine kinase inhibitors: Does surgical resection have a role?.	Population
Impact of imatinib rechallenge on health-related quality of life in patients with TKI-refractory gastrointestinal stromal tumours: Sub-analysis of the placebo-controlled, randomised phase III trial (RIGHT).	Population
Impact of L-carnitine on imatinib-related muscle cramps in patients with gastrointestinal stromal tumor.	Population
Impact of mutational status and other prognostic factors on survival in patients with advanced GIST treated with standard-dose imatinib (IM): Results from the BFR14 phase III trial of the French Sarcoma Group.	Outcome
Impact of rechallenge with imatinib in patients with advanced gastrointestinal stromal tumor after failure of imatinib and sunitinib.	Population
Impact of surgery on advanced gastrointestinal stromal tumors (GIST) in the imatinib era.	Population
Improved Efficacy of First-Line Imatinib in Advanced Gastrointestinal Stromal Tumors (GIST): The Dutch GIST Registry Data.	Outcome
Incidence and reasons for dose modification of standard-dose vs. high-dose Imatinib Mesylate (IM) in the Phase III Intergroup Study S0033 of patients (pts)	Population

with unresectable or metastatic Gastrointestinal Stromal Tumor (GIST)	
Indian experience with immunotherapy in sarcoma and gastrointestinal stromal tumors: A retrospective study.	Population
Influence of imatinib interruption and imatinib rechallenge on the residual tumor volume in patients with advanced GIST: Results of the BFR14 prospective French Sarcoma Group randomized phase III trial.	Population
Influence of imatinib interruption and rechallenge on the residual disease in patients with advanced GIST: results of the BFR14 prospective French Sarcoma Group randomised, phase III trial.	Population
Initial and late resistance to imatinib in advanced gastrointestinal stromal tumors are predicted by different prognostic factors: A European Organisation for Research and Treatment of Cancer-Italian Sarcoma Group-Australasian Gastrointestinal Trials Group Study.	Population
Initial results of phase I study of DCC-2618, a broad-spectrum KIT and PDGFRa inhibitor, in patients (pts) with gastrointestinal stromal tumor (GIST) by number of prior regimens.	Outcome
Internet-Delivered Cognitive Behavioral Therapy and Psychoeducation Program for Patients with Gastrointestinal Stromal Tumors.	Population
Interruption of imatinib (IM) in GIST patients with advanced disease: updated results of the prospective French Sarcoma Group randomized phase III trial on survival and quality of life	Population
Interruption of imatinib in advanced gastrointestinal stromal tumor after prolonged imatinib maintenance in the absence of gross tumor lesions.	Population
Interruption of imatinib in advanced gastrointestinal stromal tumor after prolonged imatinib maintenance in the absence of gross tumor lesions.	Population
Intra-patient dose escalation (IPDE) of ripretinib after disease progression in patients with advanced gastrointestinal stromal tumor (GIST): Analyses from the phase 3 INVICTUS study.	Population
Intratumoral KIT mutational heterogeneity and recurrent KIT/ PDGFRA mutations in KIT/PDGFRA wild-type gastrointestinal stromal tumors.	Outcome
INTRIGUE: eine randomisierte, offene Phase-3-Studie zur Bewertung der Wirksamkeit und Sicherheit von Ripretinib im Vergleich zu Sunitinib bei Patienten mit	Population

fortgeschrittenem gastrointestinalem Stromatumor, die zuvor mit Imatinib behandelt wurden	
INVICTUS: A phase III, interventional, double-blind, placebo-controlled study to assess the safety and efficacy of ripretinib as >= 4th-line therapy in patients with advanced gastrointestinal stromal tumors (GIST) who have received treatment with prior anticancer therapies (NCT03353753).	Population
Involvement of signaling molecules in the prediction of response to imatinib treatment in metastatic GIST patients.	Population
Is there a role for surgery in patients with "unresectable" cKIT+ gastrointestinal stromal tumors treated with imatinib mesylate?.	Population
Is there a role of surgery in patients with recurrent or metastatic gastrointestinal stromal tumours responding to imatinib: a prospective randomised trial in China.	Population
Kinase mutations and efficacy of imatinib in Korean patients with advanced gastrointestinal stromal tumors.	Population
Kinase mutations and imatinib mesylate response for 64 Taiwanese with advanced GIST: preliminary experience from Chang Gung Memorial Hospital.	Population
KIT And PDGFRA Mutations And Survival of Gastrointestinal Stromal Tumor Patients Treated With Adjuvant Imatinib in a Randomized Trial.	Population
KIT and PDGFRAmutation status and their immunohistochemical (IHC) expression profile of gastrointestinal stromal tumor (GIST) patients treated with imatinib (IMT): Seven-year single-center experience.	Outcome
KIT exon 10 variant (c.1621 A > C) single nucleotide polymorphism as predictor of GIST patient outcome.	Population
KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours.	Outcome
KIT mutations and imatinib dose effects in patients with gastrointestinal stromal tumors	Review/editorial
KIT resistance mutations identified by circulating tumor DNA and treatment outcomes in advanced gastrointestinal stromal tumor.	Population
Large-Scale, Multicenter, Prospective Registry Study of Ripretinib in Advanced GIST: A Real-World Study from China.	Outcome

Linsitinib (OSI-906) for the Treatment of Adult and Pediatric Wild-Type Gastrointestinal Stromal Tumors, a SARC Phase II Study.	Population
Long term experience of patients with unresectable or metastatic KIT positive gastrointestinal stromal tumours.	Population
Long-term adjuvant therapy for high-risk gastrointestinal stromal tumors in the real world.	Outcome
Long-term follow-up of a phase II randomized trial in advanced gastrointestinal stromal tumor (GIST) patients (pts) treated with imatinib mesylate	Population
Long-term follow-up outcome of imatinib mesylate treatment for recurrent and unresectable gastrointestinal stromal tumors.	Population
Long-term follow-up results of the multicenter phase II trial of regorafenib in patients with metastatic and/or unresectable GI stromal tumor after failure of standard tyrosine kinase inhibitor therapy.	Population
Long-Term Imatinib Treatment for Patients with Unresectable or Recurrent Gastrointestinal Stromal Tumors.	Population
Long-term outcome of dasatinib first-line treatment in gastrointestinal stromal tumor: A multicenter, 2-stage phase 2 trial (Swiss Group for Clinical Cancer Research 56/07).	Population
Long-term outcome of molecular subgroups of GIST patients treated with standard-dose imatinib in the BFR14 trial of the French Sarcoma Group.	Population
Long-term safety of regorafenib (REG) in advanced gastrointestinal stromal tumors (GIST): updated safety data of the phase 3 GRID trial.	Population
Long-term survival (over 10 years) of inoperable/metastatic GISTs: A retrospective series of 141 patients (pts) of the french sarcoma group (FSG).	Population
Long-term survival on S0033 - A phase III randomized, Intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumours (GISTS).	Population
Long-term survival outcome with tyrosine kinase inhibitors and surgical intervention in patients with metastatic or recurrent gastrointestinal stromal tumors: A 14-year, single-center experience.	Outcome
Lower-dosing ponatinib in pretreated GIST: Results of the POETIG phase II trial.	Population

Malignant gastrointestinal stromal tumors treated with imatinib in france: Efficy in real life.	Population
Malignant gastrointestinal stromal tumors treated with imatinib in France: Results in unselected patients.	Population
Malignant gastrointestinal stromal tumours treated with imatinib in France: Results in unselected patients.	Population
Management of complicated tumor response to tyrosine-kinase inhibitors in gastrointestinal stromal tumors.	Population
Management of liver metastases of gastrointestinal stromal tumors (GIST).	Population
Management of patients with gastrointestinal stromal tumor in clinical practice in Italy: A critical "event tree model" analysis of decision-making processes and outcomes.	Population
Masatinib mesylate in imatinib-naive locally advanced or metastatic gastrointestinal stromal tumor (GIST): Results of the French Sarcoma Group phase II trial.	Population
Masitinib in advanced gastrointestinal stromal tumor (GIST) after failure of imatinib: a randomized controlled open-label trial	Population
Masitinib in imatinib-naive advanced gastrointestinal stromal tumor (GIST): Five-year follow-up of the French Sarcoma Group phase II trial.	Population
Masitinib mesylate in imatinib-resistant advanced GIST: A randomized phase II trial.	Population
Meta-analysis for the association between overall survival and progression-free survival in gastrointestinal stromal tumor.	Review/editorial
Meta-Analysis of Regorafenib-Associated Adverse Events and Their Management in Colorectal and Gastrointestinal Stromal Cancers.	Review/editorial
Metastatic gastrointestinal stromal tumor: A regional cancer center experience of 44 cases.	Population
Model-Based Biomarker Selection for Dose Individualization of Tyrosine-Kinase Inhibitors.	Population
Model-based Dose Individualization of Sunitinib in Gastrointestinal Stromal Tumors.	Population
Molecular target modulation, imaging, and clinical evaluation of gastrointestinal stromal tumor patients treated with sunitinib malate after imatinib failure.	Population

Multicenter phase II trial assessing effectiveness of imatinib mesylate on relapsed or refractory KIT-positive or PDGFR-positive sarcoma.	Population
Multicenter, single-arm, two-stage phase II trial of everolimus (RAD001) with imatinib in imatinib-resistant patients (pts) with advanced GIST.	Population
Multicenter, triple-arm, single-stage, phase II trial to determine the efficacy and safety of everolimus (RAD001) in patients with refractory bone or soft tissue sarcomas including GIST.	Population
Mutation profile of drug resistant gastrointestinal stromal tumor (GIST) patients (pts) enrolled in the phase 1 study of DCC-2618.	Outcome
Mutational analysis of plasma DNA from patients (pts) in the phase III GRID study of regorafenib (REG) versus placebo (PL) in tyrosine kinase inhibitor (TKI)-refractory GIST: Correlating genotype with clinical outcomes.	Outcome
Mutational analysis of plasma DNA from patients (pts) in the phase III GRID study of regorafenib (REG) versus placebo (PL) in tyrosine kinase inhibitor (TKI)-refractory GIST: Correlating genotype with clinical outcomes.	Outcome
Mutational analysis of plasma DNA from patients (pts) in the phase III GRID study of regorafenib vs placebo in tyrosine kinase inhibitor (TKI)-refractory GIST: Correlating genotype with clinical outcomes.	Outcome
Mutational spectrum and therapy response of metastasized GIST in Central Switzerland - a population-based study.	Population
Nationwide evaluation of mutation-tailored treatment of gastrointestinal stromal tumors in daily clinical practice.	Outcome
Nationwide evaluation of mutation-tailored treatment of gastrointestinal stromal tumors in daily clinical practice.	Outcome
Nationwide trends in the incidence and outcome of patients with gastrointestinal stromal tumour in the imatinib era.	Population
Natural killer cell IFN-gamma levels predict long-term survival with imatinib mesylate therapy in gastrointestinal stromal tumor-bearing patients.	Population
Neoadjuvant tyrosine kinase inhibitors in rectal gastrointestinal stromal tumours: a provision for enhanced oncological and functional outcomes.	Population

Neurofibromatosis 1 (NF1) and gastrointestinal stromal tumors (GISTs): Five-year experience from a regional center in United Kingdom.	Outcome
Neuropsychiatric Adverse Drug Reactions with Tyrosine Kinase Inhibitors in Gastrointestinal Stromal Tumors: An Analysis from the European Spontaneous Adverse Event Reporting System.	Population
New response evaluation criteria using early morphological change in imatinib treatment for patients with gastrointestinal stromal tumor.	Population
Nilotinib in patients with GIST who failed imatinib and sunitinib: importance of prior surgery on drug bioavailability.	Population
Nilotinib in the treatment of advanced gastrointestinal stromal tumours resistant to both imatinib and sunitinib.	Outcome
Nilotinib versus imatinib as first-line therapy for patients with unresectable or metastatic gastrointestinal stromal tumours (ENESTg1): a randomised phase 3 trial.	Population
Nonadherence to imatinib treatment in patients with gastrointestinal stromal tumors: the ADAGIO study.	Population
Optimal Avapritinib Treatment Strategies for Patients with Metastatic or Unresectable Gastrointestinal Stromal Tumors.	Outcome
Outcome of metastatic GIST in the era before tyrosine kinase inhibitors.	Outcome
Outcome of patients with advanced gastro-intestinal stromal tumors (GIST) crossing over to a daily imatinib dose of 800mg (HD) after progression on 400mg (LD) - an international, intergroup study of the EORTC, ISG and AGITG	Population
Outcome of patients with advanced gastro-intestinal stromal tumours crossing over to a daily imatinib dose of 800 mg after progression on 400 mg	Population
Outcome of patients with advanced GIST achieving a complete remission (CR) with imatinib (IM) before interruption: Pooled analysis of two consecutive prospective randomizations of the French Sarcoma Group BFR14 phase III trial.	Population
Outcomes for patients with advanced GIST achieving a complete remission (CR) with imatinib (IM): results from the prospective randomized phase III trial of the French Sarcoma Group	Population

Outcomes in late-line systemic treatment in GISTs: Does sequence matter?.	Population
Outcomes of patients (pts) with advanced gastro-intestinal stromal tumors (GIST) treated with multi-kinase inhibitors other than imatinib (IM) as first-line treatment.	Outcome
Outcomes of patients with metastatic gastrointestinal stromal tumors (GIST) treated with multi-kinase inhibitors other than imatinib as first-line treatment.	Outcome
Overall survival in advanced GIST over time and correlation with access to post-imatinib tyrosine kinase inhibitors: Results from the Life Raft Group Registry.	Population
P-132 Molecular profiling of KIT and PDGFRA in Chilean GIST patients: a Latin-American perspective	Outcome
P-196 Frequency, biological behaviour and survival nomograms discrimination in non-KIT mutated gastrointestinal stromal tumors.	Outcome
Patient reported outcomes and tolerability in patients receiving ripretinib versus sunitinib after imatinib treatment in INTRIGUE: a phase 3 open-label study	Population
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	Population
Patterns of care, prognosis, and survival in patients with metastatic gastrointestinal stromal tumors (GIST) refractory to first-line imatinib and second-line sunitinib.	Population
Patterns of progression in gastrointestinal stromal tumor treated with imatinib mesylate.	Population
Pazopanib in metastatic multiply treated progressive gastrointestinal stromal tumors: Feasible and efficacious.	Population
Pazopanib plus best supportive care versus best supportive care alone in advanced gastrointestinal stromal tumours resistant to imatinib and sunitinib (PAZOGIST): a randomised, multicentre, open-label phase 2 trial.	Population
PCN84 BUDGET IMPACT ANALYSIS OF AYVAKIT (AVAPRITINIB) IN PATIENTS WITH GASTROINTESTINAL STROMAL TUMORS AND A PDGFRA EXON 18 MUTATION.	Study design
PDGRFA-mutant gastrointestinal stromal tumours (GISTs) in Eastern England: clinicopathological features	Population

and outcomes of 50 patients diagnosed between 2008-2021.	
Pharmacokinetic (PK), safety, and tolerability profile of DCC-2618 in a phase I trial supports 150mg QD selected for a pivotal phase III trial in gastrointestinal stromal tumor (GIST).	Population
Pharmacokinetic-driven phase I study of DCC-2618 a pan-KIT and PDGFR inhibitor in patients (pts) with gastrointestinal stromal tumor (GIST) and other solid tumors.	Population
Phase 1 dose-escalation study of oral tyrosine kinase inhibitor masitinib in advanced and/or metastatic solid cancers.	Population
Phase 1/1b first-in-human study of IDRX-42, a novel oral tyrosine kinase inhibitor (TKI), in patients with metastatic and/or unresectable gastrointestinal stromal tumors (GISTs).	Outcome
Phase 2 study of nilotinib as third-line therapy for patients with gastrointestinal stromal tumor.	Outcome
Phase 3, multicenter, randomized, double-blind, placebo-controlled trial of SU11248 in patients (pts) following failure of imatinib for metastatic GIST	Population
Phase I safety and pharmacokinetic study of SU-014813 in combination with docetaxel in patients with advanced solid tumours.	Population
Phase I study of olaratumab in Japanese patients with advanced solid tumors.	Population
Phase I Study of Rapid Alternation of Sunitinib and Regorafenib for the Treatment of Tyrosine Kinase Inhibitor Refractory Gastrointestinal Stromal Tumors.	Population
Phase I trial evaluating safety and efficacy of intratumorally administered inflammatory allogeneic dendritic cells (ilixadencel) in advanced gastrointestinal stromal tumors.	Population
Phase I/II study of sunitinib malate in Japanese patients with gastrointestinal stromal tumor after failure of prior treatment with imatinib mesylate.	Population
Phase Ib Trial of the Combination of Imatinib and Binimetinib in Patients with Advanced Gastrointestinal Stromal Tumors.	Population
Phase II clinical study of STI571 in Japanese (Jpn) patients (pts) with malignant gastrointestinal stromal tumors (GIST): results of the B 1201 study	Population

Phase II study of cediranib in patients with advanced gastrointestinal stromal tumors or soft-tissue sarcoma.	Population
Phase II study of dovitinib in patients with metastatic and/or unresectable gastrointestinal stromal tumours after failure of imatinib and sunitinib.	Population
Phase II study of motesanib in Japanese patients with advanced gastrointestinal stromal tumors with prior exposure to imatinib mesylate.	Population
Phase II study of oral masitinib mesilate in imatinib-naive patients with locally advanced or metastatic gastro-intestinal stromal tumour (GIST).	Outcome
Phase II Study of Ponatinib in Advanced Gastrointestinal Stromal Tumors: Efficacy, Safety, and Impact of Liquid Biopsy and Other Biomarkers.	Population
Phase II study of the HSP90-inhibitor BIIB021 in gastrointestinal stromal tumors	Population
Phase II Trial of Continuous Regorafenib Dosing in Patients with Gastrointestinal Stromal Tumors After Failure of Imatinib and Sunitinib.	Population
Phase II Trial of Imatinib Plus Binimetinib in Patients With Treatment-Naive Advanced Gastrointestinal Stromal Tumor.	Population
Phase II, open-label study of PTK787/ZK222584 for the treatment of metastatic gastrointestinal stromal tumors resistant to imatinib mesylate.	Population
Phase II, singlearm, nonrandomized, and multicenter clinical trial of regorafenib (REG) as a single agent in the firstline setting for patients with metastatic and/or unresectable KIT/PDGFR wild-type GIST. A GEIS and ISG study.	Population
Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S0033	Population
Phase III study of nilotinib versus best supportive care with or without a TKI in patients with gastrointestinal stromal tumors resistant to or intolerant of imatinib and sunitinib	Population
Phase IV Study of Sunitinib in Chinese Patients with Imatinib-Resistant or Imatinib-Intolerant Gastrointestinal Stromal Tumors.	Population
Phosphorylated-insulin growth factor I receptor (p-IGF1R) and metalloproteinase-3 (MMP3) expression in	Population

advanced gastrointestinal stromal tumors (GIST). A GEIS 19 study.	
Plasma trough concentration of imatinib and its effect on therapeutic efficacy and adverse events in Japanese patients with GIST.	Population
Platelet derived growth factor receptor alpha (PDGFRA) mutant gastrointestinal stromal tumours (GISTs): Clinicopathological characteristics and outcomes from a regional centre in the United Kingdom.	Population
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)	Population
Practical role of mutation analysis for imatinib treatment in patients with advanced gastrointestinal stromal tumors: a meta-analysis.	Review/editorial
Predicting toxicities for patients with advanced gastrointestinal stromal tumours treated with imatinib: a study of the European Organisation for Research and Treatment of Cancer, the Italian Sarcoma Group, and the Australasian Gastro-Intestinal Trials Group (EORTC-ISG-AGITG).	Population
Prediction of long-term survival in patients with metastatic gastrointestinal stromal tumor: analysis of a large, single-institution cohort.	Population
Predictive factors for long-term effects of imatinib therapy in patients with inoperable/metastatic CD117(+) gastrointestinal stromal tumors (GISTs).	Population
Predictive factors for toxicity and survival of second-line sunitinib in advanced gastrointestinal stromal tumours (GIST).	Population
Preoperative adjuvant therapy for locally advanced and recurrent/metastatic gastrointestinal stromal tumors: a retrospective study.	Outcome
Preoperative imatinib treatment in patients with locally advanced and metastatic/recurrent gastrointestinal stromal tumors: A single-center analysis.	Population
Prognostic and predictive values of KIT11-mutated grading system in patients with gastrointestinal stromal tumours A Retrospective Study.	Population
Prognostic factors after imatinib secondary resistance: survival analysis in patients with unresectable and metastatic gastrointestinal stromal tumors.	Population

Prognostic factors in gastrointestinal stromal tumors among a group of Mexican patients. [Spanish]	Population
Prognostic factors in gastrointestinal stromal tumors: Multicenter experience of 333 cases from Turkey.	Population
Prognostic stratification of high-risk gastrointestinal stromal tumors in the era of targeted therapy.	Outcome
Prognostic value of KIT/PDGFRA mutations in gastrointestinal stromal tumors: A meta-analysis.	Review/editorial
Prognostic value of the most frequent mutations in GIST: Results of the French population-based prospective study MolecGIST.	Outcome
Prognostic value of the pretreatment neutrophil-to-lymphocyte ratio in patients with advanced gastrointestinal stromal tumors treated with sunitinib after imatinib failure.	Outcome
Prognotic analysis of 132 cases with gastrointestinal stromal tumors. [Chinese]	Population
Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial	Population
Prolonged survival and disease control in the academic phase II trial of regorafenib in GIST: Response based on genotype.	Population
Prolonging Gastrointestinal-Stromal-Tumor-free life, an optimal suggestion of imatinib intervention ahead of operation.	Population
Promising antitumor activity of olverembatinib (HQP1351) in patients (pts) with tyrosine kinase inhibitor- (TKI-) resistant succinate dehydrogenase- (SDH-) deficient gastrointestinal stromal tumor (GIST)	Population
Prospective multicentric randomized phase III study of imatinib in patients with advanced gastrointestinal stromal tumors comparing interruption versus continuation of treatment beyond 1 year: the French Sarcoma Group	Population
Prospective observational study of imatinib therapy in Japanese patients with advanced gastrointestinal stromal tumors: long-term follow-up and second malignancy.	Population
PS4-3 A phase III trial of pimitespib (TAS-116) in patients with advanced gastrointestinal stromal tumor: CHAPTER-GIST-301	Population
Randomized phase 3 trial of regorafenib in patients (patients) with metastatic and/or unresectable	Population

gastrointestinal stromal tumor (GIST) progressing despite prior treatment with at least imatinib (IM) and sunitinib (SU) : grid trial	
Randomized phase III trial of imatinib (IM) rechallenge versus placebo (PL) in patients (pts) with metastatic and/or unresectable gastrointestinal stromal tumor (GIST) after failure of at least both IM and sunitinib (SU): RIGHT study.	Population
Randomized phase III trial of regorafenib in patients (pts) with metastatic and/or unresectable gastrointestinal stromal tumor (GIST) progressing despite prior treatment with at least imatinib (IM) and sunitinib (SU): GRID trial	Population
Real-World Evidence of Patient Outcome Following Treatment of Advanced Gastrointestinal Stromal Tumor (GIST) with Imatinib, Sunitinib, and Sorafenib in Publicly Funded Health Care in Poland.	Population
Real-world experience of safety and effectiveness of regorafenib for treatment of metastatic colorectal cancer, advanced gastrointestinal stromal tumors, and hepatocellular carcinoma: a post-marketing surveillance study in Korea.	Population
Regorafenib as second line therapy for imatinib-resistant gastrointestinal stromal tumor (GIST): A phase II study.	Population
Regorafenib for advanced gastrointestinal stromal tumors following imatinib and sunitinib treatment: a subgroup analysis evaluating Japanese patients in the phase III GRID trial	Population
Regorafenib treatment for advanced, refractory gastrointestinal stromal tumor:A report of the UK managed access program.	Outcome
Regorafenib treatment outcome for Taiwanese patients with metastatic gastrointestinal stromal tumors after failure of imatinib and sunitinib: a prospective, non.randomized, single.center study	Population
Regorafenib-associated adverse event management in colorectal and gastrointestinal stromal cancer patients: A systematic review and meta-analysis.	Review/editorial
Relationship between efficacy of sunitinib and KIT mutation of patients with advanced gastrointestinal stromal tumors after failure of imatinib: A systematic review.	Review/editorial
Results from a phase III trial (GRID) evaluating regorafenib (REG) in metastatic gastrointestinal stromal tumour (GIST): subgroup analysis of outcomes based on pretreatment characteristics	Population

Results from a phase III trial (GRID) evaluating regorafenib in metastatic gastrointestinal stromal tumour (GIST): subgroup analysis of outcomes based on pretreatment characteristics	Population
Resumption of imatinib to control metastatic or unresectable gastrointestinal stromal tumours after failure of imatinib and sunitinib (RIGHT): a randomised, placebo-controlled, phase 3 trial	Population
Retrospective analysis of extra-gastrointestinal stromal tumors.	Population
Retrospective analysis of the efficacy and safety of regorafenib in patients with advanced GIST.	Population
Ripretinib for advanced gastrointestinal stromal tumor: plain language summary of the INVICTUS study	Population
Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial	Population
Ripretinib intra-patient dose escalation (IPDE) following disease progression provides clinically meaningful progression-free survival (PFS) in gastrointestinal stromal tumor (GIST) in phase I study	Population
Ripretinib intrapatient dose escalation after disease progression provides clinically meaningful outcomes in advanced gastrointestinal stromal tumour.	Population
Ripretinib Versus Sunitinib in Patients With Advanced Gastrointestinal Stromal Tumor After Treatment With Imatinib (INTRIGUE): a Randomized, Open-Label, Phase III Trial	Population
S0502: A SWOG phase III randomized study of imatinib, with or without bevacizumab, in patients with untreated metastatic or unresectable gastrointestinal stromal tumors.	Population
Safety and efficacy of imatinib (STI571) in metastatic gastrointestinal stromal tumours: a phase I study	Population
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	Population
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	Population

Safety, efficacy and prognostic analyses of sunitinib in the post-marketing surveillance study of Japanese patients with gastrointestinal stromal tumor.	Population
Secondary mutations of c-KIT contribute to acquired resistance to imatinib and decrease efficacy of sunitinib in Chinese patients with gastrointestinal stromal tumors.	Population
Second-line sunitinib for Chinese patients with advanced gastrointestinal stromal tumor: 37.5 mg schedule outperformed 50 mg schedule in adherence and prognosis.	Population
Serum creatine kinase increase in patients treated with tyrosine kinase inhibitors for solid tumors.	Population
Serum Natrium Determines Outcome of Treatment of Advanced GIST with Imatinib: A Retrospective Study of 80 Patients from a Single Institution.	Population
Skin lesions in patients treated with imatinib mesylate: a 5-year prospective study.	Population
Sorafenib (SOR) in patients (pts) with imatinib (IM) and sunitinib (SU)-resistant (RES) gastrointestinal stromal tumors (GIST): Final results of a University of Chicago Phase II Consortium trial.	Outcome
Sorafenib as third- or fourth-line treatment of advanced gastrointestinal stromal tumour and pretreatment including both imatinib and sunitinib, and nilotinib: A retrospective analysis.	Population
Sorafenib in patients with metastatic gastrointestinal stromal tumors who failed two or more prior tyrosine kinase inhibitors: a phase II study of Korean gastrointestinal stromal tumors study group.	Population
Spectrum and prognostication of KIT and PDGFRA mutation in gastrointestinal stromal tumors.	Population
Standard versus personalized schedule of regorafenib in metastatic gastrointestinal stromal tumors: a retrospective, multicenter, real-world study.	Population
Starting Imatinib at 400 mg Daily in Patients with Gastrointestinal Stromal Tumors Harboring KIT Exon 9 Mutations: A Retrospective, Multicenter Study.	Population
Study on the usage, effectiveness, and toxicity associated to treatment with sorafenib. [Spanish]	Population
Subgroup analysis of Asian patients in the phase III trial (GRID) of regorafenib in pretreated metastatic gist	Population

Sunitinib as the second-line therapy for advanced GISTs after failure of imatinib in Korean patients.	Outcome
Sunitinib for Taiwanese patients with gastrointestinal stromal tumor after imatinib treatment failure or intolerance.	Population
Sunitinib in patients with imatinib-resistant gastrointestinal stromal tumor: A single center experience study.	Population
Sunitinib therapy for imatinib-resistant and/or intolerant gastrointestinal stromal tumors: comparison of safety and efficacy between standard and reduced dosage regimens.	Population
Sunitinib versus imatinib dose escalation after failure of imatinib standard dose in patients with advanced Gastrointestinal stromal tumors - a real-world multi-center study.	Population
Survival of gastrointestinal stromal tumor patients in the imatinib era: life raft group observational registry.	Population
Survival of patients with multiple primary malignancies: A study of 783 patients with gastrointestinal stromal tumor.	Population
Survival trend of advanced gastrointestinal stromal tumors treated by tyrosine kinase inhibitors: A 14-year single center experience.	Outcome
Survivin expression and its potential clinical significance in gastrointestinal stromal sarcoma.	Population
Switch Control Inhibition of KIT and PDGFRA in Patients With Advanced Gastrointestinal Stromal Tumor: A Phase I Study of Ripretinib.	Population
Symptoms reported by gastrointestinal stromal tumour (GIST) patients on imatinib treatment: combining questionnaire and forum data.	Population
Systematic review of escalated imatinib doses compared with sunitinib or best supportive care, for the treatment of people with unresectable/metastatic gastrointestinal stromal tumours whose disease has progressed on the standard imatinib dose.	Review/editorial
Taste, smell and mouthfeel disturbances in patients with gastrointestinal stromal tumors treated with tyrosine-kinase inhibitors.	Population
Ten-Year Progression-Free and Overall Survival in Patients With Unresectable or Metastatic GI Stromal Tumors: Long-Term Analysis of the European Organisation for Research and Treatment of Cancer,	Population

Italian Sarcoma Group, and Australasian Gastrointestinal Trials Group Intergroup Phase III Randomized Trial on Imatinib at Two Dose Levels.	
Ten-year review of gastrointestinal stromal tumours at a tertiary referral hospital in New Zealand.	Population
Ten-Year Survivorship in Patients with Metastatic Gastrointestinal Stromal Tumors.	Outcome
The GOLD ReGISTry: a Global, Prospective, Observational Registry Collecting Longitudinal Data on Patients with Advanced and Localised Gastrointestinal Stromal Tumours.	Population
The outcomes of patients with metastatic/inoperable gastrointestinal stromal tumors (GIST) treated with imatinib - An interim multicenter analysis of Polish Clinical GIST Registry.	Population
The potential value of F-18 FDG PET in comparison to CT in early prediction of response to imatinib (STI571) therapy in patients with gastrointestinal stromal tumors.	Population
The relationship between sunitinib exposure and both efficacy and toxicity in real-world patients with renal cell carcinoma (RCC) and gastrointestinal stromal tumour (GIST).	Population
The Role of Regorafenib in the Management of Advanced Gastrointestinal Stromal Tumors: A Systematic Review. [Review]	Review/editorial
Therapeutic drug monitoring of imatinib in patients with gastrointestinal stromal tumours - Results from daily clinical practice.	Outcome
Time course of adverse events in the phase III GRID study of regorafenib in patients with metastatic gastrointestinal stromal tumors (GIST)	Population
Time course of adverse events in the phase III GRID study of regorafenib in patients with metastatic gastrointestinal stromal tumors (GIST).	Population
Time to secondary resistance (TSR) after interruption of imatinib (IM) in advanced GIST: updated results of the prospective French Sarcoma Group randomized phase III trial on long-term survival	Population
Toxicity Management and Effectiveness of Regorafenib in Advance GIST Patients: A Real-world Study.	Population
Toxicity management of regorafenib in patients with gastro-intestinal stromal tumour (GIST) in a tertiary cancer centre.	Population

Treatment and Prognoses in Patients With Primary Gastrointestinal Stromal Tumors >=10 cm: A Single-Institution Experience in China.	Population
Treatment of advanced gastrointestinal stromal tumors in patients over 75 years old: clinical and pharmacological implications.	Population
Treatment of non-resectable and metastatic gastrointestinal stromal tumors: experience with the use of tyrosine kinase inhibitors in a third level hospital in Mexico.	Population
Treatment of patients with advanced gastrointestinal stromal tumor of small bowel: implications of imatinib mesylate	Population
Treatment outcomes in older patients with advanced gastrointestinal stromal tumor (GIST).	Outcome
Tumor growth rate analysis of progression-free survival (PFS) and overall survival (OS) for patients with metastatic and/or unresectable gastrointestinal stromal tumors (GIST) receiving placebo or regorafenib in the phase 3 GRID trial	Population
Tumor response and clinical outcome in metastatic gastrointestinal stromal tumors under sunitinib therapy: comparison of RECIST, Choi and volumetric criteria	Population
Tumor-associated tertiary lymphoid structure predicts postoperative outcomes in patients with primary gastrointestinal stromal tumors.	Population
Type and Gene Location of KIT Mutations Predict Progression-Free Survival to First-Line Imatinib in Gastrointestinal Stromal Tumors: A Look into the Exon.	Outcome
Tyrosine kinase inhibitors significantly improved survival outcomes in patients with metastatic gastrointestinal stromal tumour: a multi-institutional cohort study.	Population
Tyrosine-kinase mutations in c-KIT and PDGFR-alpha genes of imatinib naive adult patients with gastrointestinal stromal tumours (GISTs) of the stomach and small intestine: relation to tumour-biological risk-profile and long-term outcome.	Outcome
Update of phase I study of imatinib (STI571) in advanced soft tissue sarcomas and gastrointestinal stromal tumors: a report of the EORTC Soft Tissue and Bone Sarcoma Group.	Population

Updated results from a phase III trial of sunitinib in GIST patients (pts) for whom imatinib (IM) therapy has failed due to resistance or intolerance	Population
Updated results of phase 1 study of ripretinib (DCC2618), a broad-spectrum KIT and PDGFRA inhibitor, in patients with gastrointestinal stromal tumor (GIST) by line of therapy (NCT02571036).	Outcome
Use of c-KIT/PDGFRA mutational analysis to predict the clinical response to imatinib in patients with advanced gastrointestinal stromal tumours entered on phase I and II studies of the EORTC Soft Tissue and Bone Sarcoma Group.	Population
Use of imatinib mesylate in gastrointestinal stromal tumours: Pan-Birmingham Cancer Network experience.	Population
Use of PD-1 targeting, macrophage infiltration, and IDO pathway activation in sarcomas a phase 2 clinical trial.	Population
Utility of circulating tumor DNA in the management of patients with GI stromal tumor: Analysis of 243 patients.	Population
Utility values for patients with advanced gastrointestinal stromal tumors (GIST) treated with regorafenib versus placebo in the phase iii grid trial.	Population
Value of FDG-PET for monitoring treatment response in patients with advanced GIST refractory to high-dose imatinib. A multicenter GEIS study.	Population
Vatalanib for metastatic gastrointestinal stromal tumour (GIST) resistant to imatinib: final results of a phase II study.	Population
We should desist using RECIST, at least in GIST.	Population
Who are the long responders to imatinib (IM) in patients with advanced GIST? Results of the BFR14 prospective French Sarcoma Group randomized phase III trial	Population
INTRIGUE: a phase 3, randomized, open-label study to evaluate the efficacy and safety of ripretinib compared to sunitinib in patients with advanced gastrointestinal stromal tumor previously treated with imatinib [German]	Population

H.1.3 Quality assessment

For non-randomised controlled trials and observational studies, the quality assessment was evaluated using the Downs and Black checklist (93). Each item in this checklist is checked as 'yes', 'no', or 'unable to determine'. The results of the quality assessment are presented in Table 87.

Table 87 Downs and Black checklist for non-randomised controlled trials and observational studies

Question No.	Von Mehren 2018	von Mehran 2021	Cassier 2012	CSR [Avapritinib] 2021
1	Y	Y	Y	Y
2	Y	Y	Y	Y
3	Y	Y	Y	Y
4	Y	Y	Y	Y
5	N	N	N	N
6	Y	Y	Y	Y
7	N	Y	Y	Y
8	N	N	N	Y
9	N	N	N	Y

10	N	Y	Y	Y
11	U	U	U	U
12	U	U	U	U
13	N	N	N	N
14	N	N	N	N
15	N	N	N	N
16	N	N	N	N
17	N	N	Y	Y
18	N	Y	Y	Y
19	Y	Y	Y	Y
20	Y	Y	Y	Y
21	U	U	U	Y
22	Y	U	Y	Y
23	N	N	N	N
24	N	N	N	N

25	N	N	N	N
26	U	U	U	Y

For non-RCTs and obersvational studies (Downs and Black checklist) (93)

1. Is the hypothesis/aim/objective of the study clearly described?

2. Are the main outcomes to be measured clearly described in the introduction or methods section?

3. Are the characteristics of the patients included in the study clearly described?

4. Are the interventions of interest clearly described?

5. Are the distributions of principal confounders in each group of patients to be compared clearly described?

6. Are the main findings of the study clearly described?

7. Does the study provide estimates of the random variability in the data for the main outcomes?

8. Have all important adverse events that may be a consequence of the intervention been reported?

9. Have the characteristics of patients lost to follow-up been described?

10. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?

11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?

12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?

13. Were the staff, places, and facilities where the patients were treated representative of the treatment the majority of patients receive?

14. Was an attempt made to blind study subjects to the intervention they have received?

15. Was an attempt made to blind those measuring the main outcomes of the intervention?

16. If any of the results of the study were based on 'data dredging', was this made clear?

17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?

18. Were the statistical tests used to assess the main outcomes appropriate?

19. Was compliance with the intervention(s) reliable?

20. Were the main outcome measures used accurate (valid and reliable)?

21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?

22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?

23. Were study subjects randomized to intervention groups?

24. Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?

25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?

26. Were losses of patients to follow-up considered?

Abbreviations: N = No; Y = Yes; U = Unable to determine

H.1.4 Unpublished data

No unpublished literature is used to inform the clinical section of the dossier.

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

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

The SLR search aimed to address the following research questions:

- To identify utility values associated with unresectable and/or metastatic GIST harbouring the PDGFRA D842V mutation.

As detailed in Table 88, Table 89 and Table 90, the HRQoL SLR search was conducted on 23 June 2023.

The searches were performed in the following indexed databases via OVID:

- MEDLINE® and MEDLINE® In-Process (via Ovid.com)
- Embase® (via Ovid.com)
- Cochrane databases (via Ovid.com), including the following:
  - Cochrane Central Register of Controlled Trials (CCTR)
  - Cochrane Database of Systematic Reviews (CDSR)
- Evidence-based Medicine (EBM) Reviews (via Ovid.com), including the following:
  - Database of Abstracts of Reviews of Effects (DARE)
  - Health Technology Assessment (HTA)
  - National Health Service Economic Evaluation Database (NHSEED)
- Econlit (via Ovid.com)
- ScHARRHUD (via www.scharrhud.org)

Electronic searching in the literature databases was not limited according to timeframe because utility data are considered clinical outcomes for which it is generally advised not to limit electronic searching by time frame. The searches were not limited to English language.

Bibliographies of systematic reviews were screened to ensure that initial searches captured all the relevant utility studies.

In addition to the databases, proceedings of 4 conferences were searched for the last 2 years (2021–2023) to identify any studies of interest. These included:

- American Society of Clinical Oncology (ASCO) Annual meeting
- American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium
- European Society for Medical Oncology (ESMO) Congress

- International Society for Pharmacoeconomics and Outcomes Research (ISPOR)

The data identified through electronic and manual searches were supplemented by the data available on HTA websites. The following international HTA websites were searched to identify any relevant HTAs:

- National Institute for Health and Care Excellence (NICE)
- Scottish Medicines Consortium (SMC)
- All Wales Medicines Strategy Group (AWMSG)
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Gemeinsamer Bundesausschuss (GBA)
- Haute Autorite de Sante (HAS)
- Zorginstituutnederland (ZIN)
- National Centre for Pharmacoeconomics (NCPE)
- Agencia Espanola de Medicamentos y Productos Sanitarios (AEMPS)

Table 88 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Medline and Medline In-Process	Ovid	1946 – 21 June 2023	23 June 2023
Embase	Ovid	1974 – 21 June 2023	23 June 2023
CCTR	Ovid	From May 2023	23 June 2023
CDSR	Ovid	2005 – 20 June 2023	23 June 2023
DARE	Ovid	1st Quarter 2016	23 June 2023
HTA	Ovid	4th Quarter 2016	23 June 2023
NHSEED	Ovid	1st Quarter 2016	23 June 2023
Econlit	Ovid	1886 – June 15 2023	23 June 2023
ScHARRHUD	ScHARRUD webpage	Unlimited	23 June 2023

Abbreviations: CCTR = Cochrane Central Register of Controlled Trials; CDSR = Cochrane Database of Systematic Reviews; DARE = Database of Abstracts of Reviews of Effects; HTA = Health Technology Assessment; NHSEED = National Health Service Economic Evaluation Database.

Table 89 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
NICE	www.nice.org.uk		23 June 2023

Source name	Location/source	Search strategy	Date of search
SMC	https://www.scottishmedicines.org.uk/home	gastrointestinal gastro-intestinal gastro intestinal gastrointestinal stromal stromal gist	23 June 2023
AWMSG	https://awttc.nhs.wales/	gastrointestinal gastro-intestinal gastro intestinal gastrointestinal stromal stromal gist	23 June 2023
CADTH	https://www.cadth.ca/search	gastrointestinal gastro-intestinal gastro intestinal gastrointestinal stromal stromal gist	23 June 2023
GBA	https://www.g-ba.de/english/	gastrointestinal gastro-intestinal gastro intestinal gastrointestinal stromal stromal gist	23 June 2023
HAS	https://www.has-sante.fr/jcms/p_3291681/en/hta-the-has-a-lead-player-in-the-european-cooperation-for-health-technology-assessment	gastrointestinal gastro-intestinal gastro intestinal gastrointestinal stromal stromal gist	23 June 2023
ZIN	https://english.zorginstituutnederland.nl/	gastrointestinal gastro-intestinal gastro intestinal gastrointestinal stromal stromal	23 June 2023

Source name	Location/source	Search strategy	Date of search
		gist	
NCPE	https://www.ncpe.ie/submission-process/hta-guidelines/	gastrointestinal gastro-intestinal gastro intestinal gastrointestinal stromal stromal gist	23 June 2023
AEMPS	https://www.aemps.gob.es/informa-en/the-spanish-agency-of-medicines-and-medical-devices-aemps-recommends-using-voluntary-harmonisation-procedure-before-the-official-submission-of-a-multi-state-ct-application/?lang=en	gastrointestinal gastro-intestinal gastro intestinal gastrointestinal stromal stromal gist	23 June 2023

Abbreviations: NICE = National Institute for Health and Care Excellence; CADTH = Canadian Agency for Drugs and Technologies in Health; SMC = Scottish Medicines Consortium; AWMSG = All Wales Medicines Strategy Group; GBA = Gemeinsamer Bundesausschuss; HAS = Haute Autorite de Sante; ZIN = Zorginstituutnederland; NCPE = National Centre for Pharmacoeconomics; AEMPS = Agencia Espanola de Medicamentos y Productos Sanitarios

Table 90 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
ASCO General meeting	https://meetings.asco.org/abstracts-presentations/search?query=*&q=*&sortBy=AbstractBrowse&filters=%7B%22presentationType%22:%5B%7B%22key%22:%22Abstract%20Presentation%22%7D,%7B%22key%22:%22Poster%22%7D,%7B%22key%22:%22Abstract%22%7D%5D,%22meetingTypeName%22:%5B%7B%22key%22:%22ASCO%20Annual%20Meeting%22%7D%5D,%22meetingYear%22:%5B%7B%22key%22:%222021%22%7D%5D%7D&size=50	Electronic search	gastrointestinal gastro-intestinal gastro intestinal gastrointestinal stromal gist	23 June 2023

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
ASCO Gastrointestinal Cancers Symposium	https://meetings.asco.org/abstracts-presentations/search?query=*&q=*&sortBy=AbstractBrowse&filters=%7B%22presentationType%22:%5B%7B%22key%22:%22Abstract%20Presentation%22%7D,%7B%22key%22:%22Poster%22%7D,%7B%22key%22:%22Abstract%22%7D%5D,%22meetingYear%22:%5B%7B%22key%22:%222021%22%7D%5D,%22meetingTypeName%22:%5B%7B%22key%22:%22Gastrointestinal%20Cancers%20Symposium%22%7D%5D%7D&size=50	Electronic search	gastrointestinal gastro-intestinal gastro intestinal gastrointestinal stromal gist	23 June 2023
ESMO	https://oncologypro.esmo.org/meeting-resources/esmo-congress	Electronic search	gastrointestinal gastro-intestinal gastro intestinal gastrointestinal stromal gist	23 June 2023
ISPOR	https://www.ispor.org/heor-resources/presentations-database/search	Electronic search	gastrointestinal gastro-intestinal gastro intestinal gastrointestinal stromal gist	23 June 2023

Abbreviations: ASCO = American Society of Clinical Oncology; ESMO = European Society of Medical Oncology; ISPOR = International Society for Pharmacoeconomics and Outcomes Research

I.1.1 Search strategies

All SLR search algorithms were generated using population, interventions/comparators, outcomes, study design, and time period (PICOS-T)-related elements outlined in Table 91 below. These were generated from the research question pertinent to each section.

Bibliographies of additional, published, relevant systematic review articles were examined to obtain references. Bibliographies of accepted studies were reviewed to obtain further relevant references.

In the first pass, each abstract was reviewed by two independent investigators as to its suitability for inclusion in the study according to the above-defined selection criteria. Discrepancies were resolved by a third investigator. For abstracts that were deemed relevant during the first-level review, full-text articles were retrieved and reviewed.

In the second pass, the full-text version of each publication accepted in the first pass was reviewed by one investigator. All publications rejected at this stage were reviewed by a second investigator to confirm the rejection decision. For each excluded study, a specific reason for exclusion was provided and validated by a second investigator. A third investigator was consulted to resolve disagreements where necessary.

Data extraction was performed in the following steps:

3. Information from the full-text articles was extracted independently into data extraction forms by one investigator.
4. Data extraction was independently validated by a second investigator; a third investigator was consulted to resolve disagreements as necessary.

Publications reporting duplicate results were not extracted into the data extraction table.

Table 91 Inclusion and exclusion criteria for utilities SLR

PICOS-T	Inclusion criteria	Exclusion criteria
Population	Adult (age ≥18 years) patients with unresectable GIST and with the PDGFRA D842V mutation regardless of previous therapy	• Healthy volunteers • Paediatric population • Disease other than PDGFRA D842V mutation
Intervention	No limits	None
Comparators	No limits	None
Outcomes	All types of utilities data including health state utility data, disutilities, mapping from QoL (i.e., SF-36), etc.	Studies not reporting utility values
Study design	• Studies reporting utility data • Economic evaluations reporting patients' utility values • Systematic reviews*	• Letters, comments, and editorials • Case series or case reports
Language	No limits	None
Countries	No limits	None

Time limit	No limits	None

Abbreviations: GIST = gastrointestinal stromal tumour; QoL = quality of life; PDGFRA = platelet-derived growth factor receptor alpha.

Note: * Bibliographies of systematic review articles were screened to ensure that all relevant studies are identified in the SLR.

Table 92 to Table 97 present the search hits in Medline, Embase, Cochrane databases, EBM, Econlit and ScHARRHUD.

Table 92 Search strategy for Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations

No.	Query	Results
#1	exp Gastrointestinal Stromal Tumors/	7,687
#2	("gastrointestinal stromal tumour*" or "gastrointestinal stromal tumor*" or "gastro-intestinal stromal tumour*" or "gastro-intestinal stromal tumor*" or gist).tw.	12,960
#3	1 or 2	13,896
#4	exp "Quality of Life"/	267,775
#5	exp "Value of Life"/	5,806
#6	exp Quality-Adjusted Life Years/	15,680
#7	exp "Surveys and Questionnaires"/	1,210,217
#8	exp Health Surveys/	623,533
#9	exp Health Status/	438,860
#10	exp Health Status Indicators/	342,146
#11	exp Self Report/	43,067
#12	exp Disability Evaluation/	56,360
#13	exp Models, Economic/	16,214
#14	exp Visual Analog Scale/	4,109
#15	(qol or (quality adj2 life) or (value adj2 (money or monetary)) or "life quality" or "life qualities" or utility or utilities or disutility or disutilities or "well being" or wellbeing or "quality adjusted" or "adjusted life" or "life year" or "life years" or qaly* or qald* or qale* or qtime* or "disability adjusted life" or daly* or "short form*" or shortform* or shorform or shortfrom or sf* or euroqol* or "euro qol*" or eq5d or "eq 5d" or "eq5-d" or euroqual* or "euro qual*" or "eq-sdq" or eqsdq or hql or hrql or hqol or "h qol" or hrqol or "hr qol" or "health* year* equivalent*" or hye or hyes or (health adj3 (status or index)) or hui or hui1 or hui2 or "hui-2"	1,206,121

No.	Query	Results
	or hui3 or "hui-3" or HSUV or HSUVs or rosser or (quality adj2 (wellbeing or "well being")) or qwb or (willingness adj2 pay) or wtp or (patient adj1 report*) or "standard gamble*" or (standard adj1 gamble*) or "time trade off" or "time tradeoff" or timetradeoff or tto or "visual analog* scale" or vas or vas10 or "vas 10").mp.	
#16	(preference* adj3 (score* or scoring or valu* or measur* or evaluat* or scale* or instrument* or weight or weights or weighting or information or data or unit or units or health* or life or estimat* or elicit* or disease* or mean or cost* or expenditure* or gain or gains or loss or losses or lost or analysis or index* or indices or overall or reported or calculat* or range* or increment* or state or states or status)).mp.	27,421
#17	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	2,315,633
#18	3 and 17	559
#19	("Case Reports" or Comment or Editorial or Letter).pt.	4,280,948
#20	exp Animals/ not (exp Animals/ and exp Humans/)	5,132,387
#21	19 or 20	9,302,708
#22	18 not 21	460

Table 93 Search strategy for Embase

No.	Query	Results
#1	exp gastrointestinal stromal tumor/	21,097
#2	("gastrointestinal stromal tumour*" OR "gastrointestinal stromal tumor*" OR "gastro-intestinal stromal tumour*" OR "gastro-intestinal stromal tumor*" OR gist).tw.	20,181
#3	#1 OR #2	26,279
#4	exp "quality of life"/	651,171
#5	exp socioeconomics/	1,317,955
#6	exp quality adjusted life year/	35,593
#7	exp questionnaire/	922,677
#8	exp health survey/	268,113
#9	exp health status/	310,369

No.	Query	Results
#10	exp health status indicator/	41,239
#11	exp self report/	153,283
#12	exp Nottingham Health Profile/	652
#13	exp Sickness Impact Profile/	2,375
#14	exp disability assessment/	45,676
#15	exp economic model/	3,764
#16	exp visual analog scale/	123,433
#17	(qol or (quality adj2 life) or (value adj2 (money or monetary)) or "life quality" or "life qualities" or utility or utilities or disutility or disutilities or "well being" or wellbeing or "quality adjusted" or "adjusted life" or "life year" or "life years" or qaly* or qald* or qale* or qtime* or "disability adjusted life" or daly* or "short form*" or shortform* or shorform or shortfrom or sf* or euroqol* or "euro qol*" or eq5d or "eq 5d" or "eq5-d" or euroqual* or "euro qual*" or "eq-sdq" or eqsdq or hql or hrql or hqol or "h qol" or hrqol or "hr qol" or "health* year* equivalent*" or hye or hyes or (health adj3 (status or index)) or hui or hui1 or hui2 or "hui-2" or hui3 or "hui-3" or HSUV or HSUVs or rosser or (quality adj2 (wellbeing or "well being")) or qwb or (willingness adj2 pay) or wtp or (patient adj1 report*) or "standard gamble*" or (standard adj1 gamble*) or "time trade off" or "time tradeoff" or timetradeoff or tto or "visual analog* scale" or vas or vas10 or "vas 10").mp.	1,882,852
#18	(preference* adj3 (score* or scoring or valu* or measur* or evaluat* or scale* or instrument* or weight or weights or weighting or information or data or unit or units or health* or life or estimat* or elicit* or disease* or mean or cost* or expenditure* or gain or gains or loss or losses or lost or analysis or index* or indices or overall or reported or calculat* or range* or increment* or state or states or status)).mp.	36,818
#19	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	4,009,259
#20	3 and 19	2,006
#21	(Editorial or Letter or Note).pt.	3,035,648
#22	"case report*".ti.	404,355
#23	exp animal/ not (exp animal/ and exp human/)	5,193,833
#24	21 or 22 or 23	8,548,354
#25	20 not 24	1,845

Table 94 Search strategy for CCTR and CDSR

No.	Query	Results
#1	exp Gastrointestinal Stromal Tumors/	212
#2	("gastrointestinal stromal tumour*" or "gastrointestinal stromal tumor*" or "gastro-intestinal stromal tumour*" or "gastro-intestinal stromal tumor*" or gist).tw.	718
#3	1 or 2	745
#4	exp "Quality of Life"/	42,474
#5	exp "Value of Life"/	46
#6	exp Quality-Adjusted Life Years/	1,932
#7	exp "Surveys and Questionnaires"/	70,003
#8	exp Health Surveys/	36,756
#9	exp Health Status/	50,934
#10	exp Health Status Indicators/	26,864
#11	exp Self Report/	3,982
#12	exp Disability Evaluation/	4,306
#13	exp Models, Economic/	571
#14	exp Visual Analog Scale/	5,167
#15	(qol or (quality adj2 life) or (value adj2 (money or monetary)) or "life quality" or "life qualities" or utility or utilities or disutility or disutilities or "well being" or wellbeing or "quality adjusted" or "adjusted life" or "life year" or "life years" or qaly* or qald* or qale* or qtime* or "disability adjusted life" or daly* or "short form*" or shortform* or shorform or shortfrom or sf* or euroqol* or "euro qol*" or eq5d or "eq 5d" or "eq5-d" or euroqual* or "euro qual*" or "eq-sdq" or eqsdq or hql or hrql or hqol or "h qol" or hrqol or "hr qol" or "health* year* equivalent*" or hye or hyes or (health adj3 (status or index)) or hui or hui1 or hui2 or "hui-2" or hui3 or "hui-3" or HSUV or HSUVs or rosser or (quality adj2 (wellbeing or "well being")) or qwb or (willingness adj2 pay) or wtp or (patient adj1 report*) or "standard gamble*" or (standard adj1 gamble*) or "time trade off" or "time tradeoff" or timetradeoff or tto or "visual analog* scale" or vas or vas10 or "vas 10").mp.	282,745
#16	(preference* adj3 (score* or scoring or valu* or measur* or evaluat* or scale* or instrument* or weight or weights or weighting or information	4,571

No.	Query	Results
	or data or unit or units or health* or life or estimat* or elicit* or disease* or mean or cost* or expenditure* or gain or gains or loss or losses or lost or analysis or index* or indices or overall or reported or calculat* or range* or increment* or state or states or status)).mp.	
#17	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	340,487
#18	3 and 17	101
#19	CDSR	8
#20	CCTR	93

Table 95 Search strategy for DARE, HTA and NHSEED

No.	Query	Results
#1	("gastrointestinal stromal tumour*" or "gastrointestinal stromal tumor*" or "gastro-intestinal stromal tumour*" or "gastro-intestinal stromal tumor*" or gist).tw.	67
#2	1 or 2	67
#3	DARE	30
#4	HTA	25
#5	NHSEED	12

Table 96 Search strategy for Econlit

No.	Query	Results
#1	("gastrointestinal stromal tumour*" or "gastrointestinal stromal tumor*" or "gastro-intestinal stromal tumour*" or "gastro-intestinal stromal tumor*" or gist).tw.	54

Table 97 Search strategy for ScHARRHUD

No.	Query	Results
#1	Gastro-intestinal stromal or gastrointestinal stromal	0

The PRISMA flow diagram of the HRQoL SLR is presented in Figure 58 below. Among the 2527 publications initially identified and screened from multiple databases, 2464 were excluded, leaving 63 publications for further evaluation of eligibility. However, upon assessment, all the studies were deemed ineligible for inclusion, resulting in none being included in the final SLR.

Table 98 provides an overview of the publications excluded with reasons.

Table 98 Overview of publications excluded at full-text screening from the health-related quality of life SLR

No.	Publication	Exclusion reason
#1	A pharmaco-economic analysis of second-line treatment with imatinib or sunitinib in patients with advanced gastrointestinal stromal tumours.	Population
#2	A randomised phase 2 study of continuous or intermittent dosing schedule of imatinib re-challenge in patients with tyrosine kinase inhibitor-refractory gastrointestinal stromal tumours.	Population
#3	Adherence to Adjuvant Imatinib Therapy in Patients with Gastrointestinal Stromal Tumor in Clinical Practice: A Cross-Sectional Study.	Population
#4	Assessment of adherence to imatinib and health-related quality of life among patients with gastrointestinal stromal tumor: A cross-sectional study in an oncology clinic in malaysia.	Population
#5	Clinical effectiveness and cost-effectiveness of imatinib dose escalation for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours that have progressed on treatment at a dose of 400 mg/day: a systematic review and economic evaluation (Provisional abstract)	Review/editorial
#6	Cost effectiveness of imatinib mesylate in the treatment of advanced gastrointestinal stromal tumours.	Population
#7	Cost-Effectiveness Analysis of Fourth- or Further-Line Ripretinib in Advanced Gastrointestinal Stromal Tumors	Population
#8	Cost-effectiveness Analysis of Genetic Testing and Tailored First-Line Therapy for Patients with Metastatic Gastrointestinal Stromal Tumors	Population
#9	Cost-Effectiveness Analysis of Regorafenib for Gastrointestinal Stromal Tumour (GIST) in Germany.	Population

#10	Cost-effectiveness analysis of sunitinib in patients with metastatic and/or unresectable gastrointestinal stroma tumours (GIST) after progression or intolerance with imatinib	Population
#11	Cost-Effectiveness Analysis of Tyrosine Kinase Inhibitors in Gastrointestinal Stromal Tumor: A Systematic Review.	Review/editorial
#12	Effect of regorafenib in delaying definitive deterioration in health-related quality of life in patients with advanced cancer of three different tumor types	Population
#13	Fear of progression in patients with gastrointestinal stromal tumors (GIST): Is extended lifetime related to the Sword of Damocles?.	Population
#14	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	Population
#15	Health utility of patients with advanced gastrointestinal stromal tumors (GIST) after failure of imatinib and sunitinib: findings from GRID, a randomized, double-blind, placebo-controlled phase III study of regorafenib versus placebo	Population
#16	Health-Related Quality of Life and Side Effects in Gastrointestinal Stromal Tumor (GIST) Patients Treated with Tyrosine Kinase Inhibitors: A Systematic Review of the Literature.	Review/editorial
#17	Imatinib for the treatment of patients with unresectable and/or metastatic gastrointestinal stromal tumours: Systematic review and economic evaluation.	Review/editorial
#18	Impact of imatinib rechallenge on health-related quality of life in patients with TKI-refractory gastrointestinal stromal tumours: sub-analysis of the placebo-controlled, randomised phase III trial (RIGHT)	Population
#19	Impact of l-carnitine on imatinib-related muscle cramps in patients with gastrointestinal stromal tumor	Population
#20	Internet-Delivered Cognitive Behavioral Therapy and Psychoeducation Program for Patients with Gastrointestinal Stromal Tumors	Population
#21	Interruption of imatinib (IM) in GIST patients with advanced disease: updated results of the prospective French Sarcoma Group randomized phase III trial on survival and quality of life	Population
#22	Optimizing the dose in patients treated with imatinib as first line treatment for gastrointestinal stromal tumours: A cost-effectiveness study.	Population

#23	Patient reported outcomes and tolerability in patients receiving ripretinib versus sunitinib after imatinib treatment in INTRIGUE: a phase 3 open-label study	Population
#24	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	Population
#25	Phase II clinical trial with pegylated liposomal doxorubicin (CAELYX®/Doxil®) and quality of life evaluation (EORTC QLQ-C30) in adult patients with advanced soft tissue sarcomas: a study of the Spanish Group for Research in Sarcomas (GEIS)	Population
#26	Prospective multicentric randomized phase III study of imatinib in patients with advanced gastrointestinal stromal tumors comparing interruption versus continuation of treatment beyond 1 year: the French Sarcoma Group	Population
#27	Psychological and social challenges of patients with locally advanced and metastatic gastrointestinal stromal tumours (GIST) on long-term treatment with tyrosine kinase inhibitors: a qualitative study with patients and medical oncologists.	Population
#28	Psychological Distress, Fatigue and Quality of Life in Patients with Gastrointestinal Stromal Tumors.	Population
#29	Quality of life (QoL) and self-reported function with ripretinib in ≥4th-line therapy for patients with gastrointestinal stromal tumors (GIST): analyses from INVICTUS	Population
#30	Quality of life of GIST patients with and without current tyrosine kinase inhibitor treatment: Cross-sectional results of a German multicentre observational study (PROSa).	Population
#31	Resistance training as supportive measure in advanced cancer patients undergoing TKI therapy-a controlled feasibility trial.	Population
#32	Re-validation and screening capacity of the 6-item version of the Cancer Worry Scale.	Population
#33	Ripretinib for advanced gastrointestinal stromal tumor: Plain language summary of the INVICTUS study.	Population
#34	Ripretinib Versus Sunitinib in Patients With Advanced Gastrointestinal Stromal Tumor After Treatment With Imatinib (INTRIGUE): A Randomized, Open-Label, Phase III Trial.	Population
#35	Safety profile of ripretinib, including impact of alopecia, and Palmar-Plantar Erythrodysesthesia Syndrome	Population

	(PPES) on patient-reported outcomes (PROs), in ≥ fourth-line advanced gastrointestinal stromal tumors (GIST): analyses from INVICTUS	
#36	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.	Population
#37	Second-line sunitinib for Chinese patients with advanced gastrointestinal stromal tumor: 37.5 mg schedule outperformed 50 mg schedule in adherence and prognosis.	Population
#38	Self-reported cognitive impairments and quality of life in patients with gastrointestinal stromal tumor: Results of a multinational survey.	Population
#39	Severe fatigue in GIST patients: Prevalence, impact and factors associated with fatigue.	Population
#40	Single-port versus standard laparoscopic resection for a gastric benign tumor in gastroscopic-laparoscopic rendezvous procedures using a laser-supported diaphanoscopy.	Population
#41	Skin lesions in patients treated with imatinib mesylate: a 5-year prospective study.	Population
#42	Smartphone-Based Ecological Momentary Assessment for the Measurement of the Performance Status and Health-Related Quality of Life in Cancer Patients Under Systemic Anticancer Therapies: Development and Acceptability of a Mobile App.	Population
#43	Sunitinib for the treatment of gastrointestinal stromal tumours: a critique of the submission from Pfizer.	Population
#44	Surgical and combined treatment of patients with duodenal stromal tumors. [Russian]	Population
#45	Survival in advanced GIST has improved over time and correlates with increased access to post-imatinib tyrosine kinase inhibitors: Results from Life Raft Group Registry.	Study design
#46	Symptom burden in gastrointestinal stromal tumors (GIST).	Population
#47	Symptoms from treatment with sunitinib or sorafenib: A multicenter explorative cohort study to explore the influence of patient-reported outcomes on therapy decisions.	Population
#48	Symptoms in gastrointestinal stromal tumors.	Population

#49	Symptoms reported by gastrointestinal stromal tumour (GIST) patients on imatinib treatment: combining questionnaire and forum data.	Population
#50	Systematic review of escalated imatinib doses compared with sunitinib or best supportive care, for the treatment of people with unresectable/metastatic gastrointestinal stromal tumours whose disease has progressed on the standard imatinib dose.	Review/editorial
#51	Taste, smell and mouthfeel disturbances in patients with gastrointestinal stromal tumors treated with tyrosine-kinase inhibitors.	Population
#52	The association of polypharmacy with functional status impairments, frailty, and health-related quality of life in older adults with gastrointestinal malignancy - Results from the Cancer and Aging Resilience Evaluation (CARE) registry.	Population
#53	The clinical characteristics and the role of surgery and imatinib treatment in patients with liver metastases from c-Kit positive gastrointestinal stromal tumors (GIST).	Population
#54	The economic impact of cytoreductive surgery and tyrosine kinase inhibitor therapy in the treatment of advanced gastrointestinal stromal tumours: A Markov chain decision analysis.	Population
#55	The epidemiologic, health-related quality of life, and economic burden of gastrointestinal stromal tumours.	Review/editorial
#56	The Randomized AMBORA Trial: Impact of Pharmacological/Pharmaceutical care on medication safety and patient-reported outcomes during treatment with new oral anticancer agents.	Population
#57	The short-term effect of endoscopic submucosal dissection on gastric stromal tumors and its effect on immune function.	Population
#58	The use of cost per life year gained as a measurement of cost-effectiveness in Spain: A systematic review of recent publications.	Review/editorial
#59	Transferability of Health-Related Quality of Life Data of Large Observational Studies to Clinical Practice: Comparing Retroperitoneal Sarcoma Patients from the PROSa Study to a TARPS-WG Cohort.	Population
#60	Treatment of gastrointestinal tumor (GIST) of the rectum requiring abdominoperineal resection following neoadjuvant imatinib: A cost-effectiveness analysis.	Population
#61	Tyrosine kinase inhibitors significantly improved survival outcomes in patients with metastatic	Population

	gastrointestinal stromal tumour: A multi-institutional cohort study.	
#62	Utility values for patients with advanced gastrointestinal stromal tumors (GIST) treated with regorafenib versus placebo in the phase iii grid trial.	Population
#63	Verification of imatinib cost-effectiveness in advanced gastrointestinal stromal tumor in British Columbia (VINCE-BC study).	Population

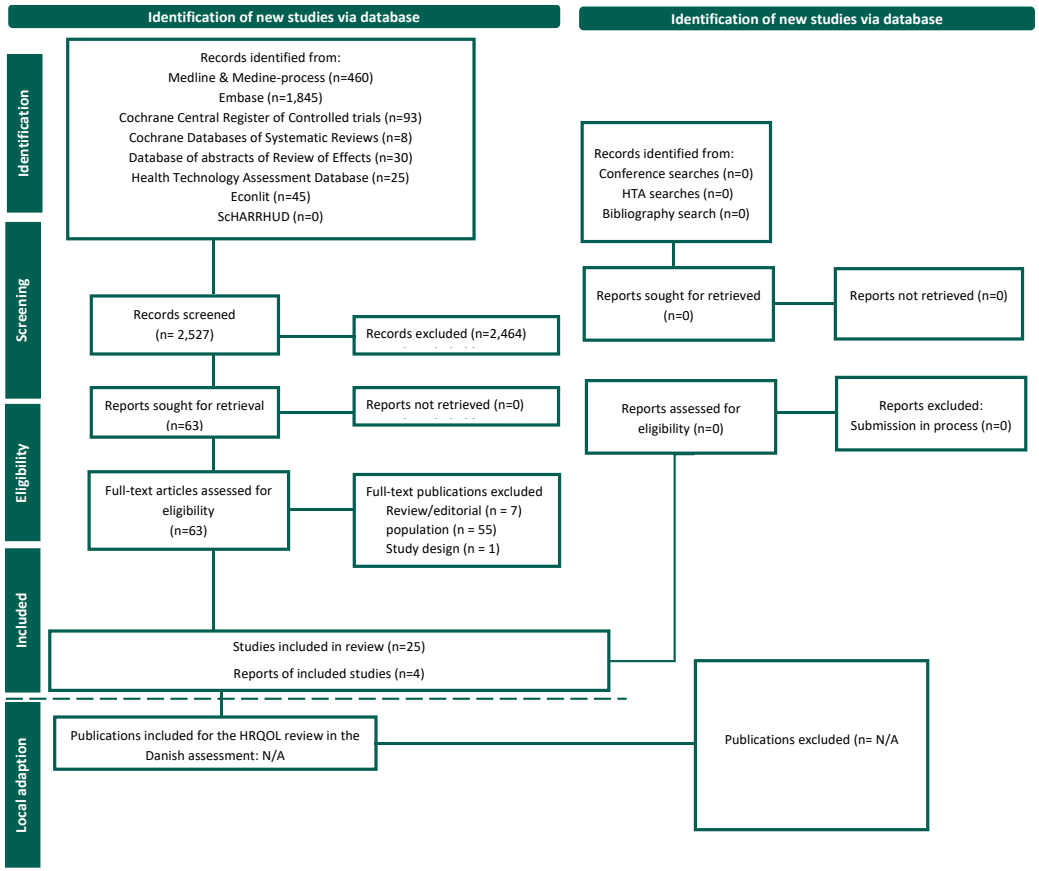

Figure 58 HRQoL PRISMA flow diagram

I.1.2 Quality assessment and generalizability of estimates

Not applicable as not studies were identified.

I.1.3 Unpublished data

N/A

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

N/A

At the time of writing this submission dossier, a SLR on health economic models was not conducted in time to accommodate the new DMC submission template.

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